



This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

- + *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.
- + *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.
- + *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.
- + *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at <http://books.google.com/>

LANE MEDICAL LIBRARY STANFORD
J53 .T56 1877
A treatise on the pathology of the urine



24503412845

LANE



GAL

LIBRARY

COOPER LANE FUND

A TREATISE
ON THE
PATHOLOGY OF THE URINE

22c

A T R E A T I S E
ON THE
PATHOLOGY OF THE URINE

INCLUDING
A COMPLETE GUIDE TO ITS ANALYSIS

LANE LIBRARY
BY

J. L. W. THUDICHUM, M.D.

Second Edition



LONDON



J. & A. CHURCHILL, NEW BURLINGTON STREET

1877

[All rights reserved.]

TABLE I

T53
1877

TO

JOHN SIMON, Esq., C.B., F.R.S.,

LATE MEDICAL OFFICER OF THE PRIVY COUNCIL AND LOCAL GOVERNMENT BOARD,
MEMBER OF THE MEDICAL COUNCIL OF EDUCATION AND REGISTRATION, ETC.,

This Work is Respectfully Inscribed,

AS A SMALL TRIBUTE OF ADMIRATION FOR HIS MANY AND EMINENT
PUBLIC SERVICES

IN MAINTAINING AND IMPROVING THE HEALTH OF THE PEOPLE,
AND FOR HIS UNTIRING AND GENEROUS EFFORTS IN ADVANCING SANITARY
AND MEDICAL SCIENCE BY ORIGINAL RESEARCHES,

BY HIS GRATEFUL FRIEND,

The Author.



CONTENTS.

	PAGE
CHAPTER I.	
GENERAL CHARACTERS OF URINE,	1
CHAPTER II.	
QUANTITY OF URINE AND INGREDIENTS,	14
CHAPTER III.	
UREA, $\text{CH}_4\text{N}_2\text{O}$,	29
CHAPTER IV.	
URIC ACID, $\text{C}_5\text{H}_4\text{N}_4\text{O}_3 + 2\text{H}_2\text{O}$,	56
CHAPTER V.	
XANTHINE, $\text{C}_5\text{H}_4\text{N}_4\text{O}_2$,	94
CHAPTER VI.	
HYPOXANTHINE, $\text{C}_5\text{H}_4\text{N}_4\text{O}$,	107
CHAPTER VII.	
GUANINE, $\text{C}_5\text{H}_4\text{N}_6\text{O}$,	115
CHAPTER VIII.	
KREATININE, $\text{C}_4\text{H}_7\text{N}_3\text{O}$,	122
CHAPTER IX.	
REDUCINE, $\text{C}_6\text{H}_{11}\text{N}_3\text{O}_4$,	139
CHAPTER X.	
HIPPURIC ACID, $\text{C}_9\text{H}_9\text{NO}_3$,	144

	PAGE
CHAPTER XI.	
INDIGOGEN, URRHODINOGEN,	167
CHAPTER XII.	
PYROCATECHIN, $C_6H_6O_2$,	187
CHAPTER XIII.	
PHENOL-PRODUCING SUBSTANCES. — PHENOL-SULPHURIC ACID, $C_6H_6SO_4$,	190
CHAPTER XIV.	
CRESOL-PRODUCING SUBSTANCES,	200
CHAPTER XV.	
CHROMOGEN OF UROBILINE,	207
CHAPTER XVI.	
OMICHMYL-OXYDE,	210
CHAPTER XVII.	
URERYTHRINE,	212
CHAPTER XVIII.	
UROCHROME,	217
CHAPTER XIX.	
ACETIC AND FORMIC ACID,	247
CHAPTER XX.	
KRYPTOPHANIC ACID, $C_8H_9NO_6$,	255
CHAPTER XXI.	
CARBONIC ACID, CO_2 ,	268
CHAPTER XXII.	
CHLORINE AND CHLORIDES OF SODIUM AND POTASSIUM,	271
CHAPTER XXIII.	
SULPHURIC ACID AND SULPHATES,	285
CHAPTER XXIV.	
HYPOSCLPHEUROUS ACID, S_2O_2 , AND SULPHUROUS ACID, SO_2 ,	293

CONTENTS.

ix

PAGE

CHAPTER XXV.

HYDROTHION, H_2S , AND HYDRO-SULPHOCYANIC ACID, $CNSH$, 298

CHAPTER XXVI.

PHOSPHORIC ACID AND PHOSPHATES, 303

CHAPTER XXVII.

AMMONIA, NH_3 , 313

CHAPTER XXVIII.

TRIMETHYLAMINE, C_3H_9N , 319

CHAPTER XXIX.

POTASSIUM AND SODIUM, 321

CHAPTER XXX.

CALCIUM AND MAGNESIUM, 327

CHAPTER XXXI.

IRON, 341

CHAPTER XXXII.

ANATOMICAL ELEMENTS OF BLOOD, 346

CHAPTER XXXIII.

HEMATOCRYSTALLINE AND HEMATINE, 352

CHAPTER XXXIV.

CRUENTURESIS, 358

CHAPTER XXXV.

UROCRUBROHEMATINE AND UROFUSCOHEMATINE, 363

CHAPTER XXXVI.

FIBRINOUS, LYMPHATIC, OR CHYLOUS URINE, 368

CHAPTER XXXVII.

ALBUMEN, 373

CHAPTER XXXVIII.

CASTS OF URINIFEROUS TUBULES, 382

	PAGE
CHAPTER XXXIX.	
FAT AND OIL ; UROSTEALITH,	386
CHAPTER XL.	
MUCUS,	388
CHAPTER XLI.	
PUS,	390
CHAPTER XLII.	
THE FERMENT OF UREA AND URINE,	394
CHAPTER XLIII.	
CANCER CELLS AND TUBERCULAR MATTER,	398
CHAPTER XLIV.	
CYSTICERCUS TÆNIÆ ECHINOCOCCUS,	399
CHAPTER XLV.	
SPERMATIC FILAMENTS OR SPERMATOOA,	405
CHAPTER XLVI.	
SARCINA VENTRICULI,	407
CHAPTER XLVII.	
COLOURING MATTERS OF BILE,	408
CHAPTER XLVIII.	
BILIARY ACIDS,	415
CHAPTER XLIX.	
GRAPE SUGAR, $C_6H_{12}O_6$,	425
CHAPTER L.	
DEXTRENE, $C_6H_{10}O_5$,	450
CHAPTER LI.	
INOSITE, $C_6H_{12}O_6$,	452
CHAPTER LII.	
LACTIC ACID, $C_3H_5O_3$,	456

CONTENTS.	xi
	PAGE
CHAPTER LIII.	
DINITROGENISED DERIVATE OF SARCOLACTIC ACID, $C_3H_5N_2O$,	467
CHAPTER LIV.	
CYSTINE, $C_3H_5NSO_2$,	470
CHAPTER LV.	
ALCOHOL, C_2H_5O ,	476
CHAPTER LVI.	
ACETONE, C_3H_6O ,	488
CHAPTER LVII.	
ALLANTOINE, $C_4H_6N_4O_3$,	493
CHAPTER LVIII.	
OXALURIC ACID, $C_3H_4N_2O_4$,	497
CHAPTER LIX.	
OXALIC ACID, $C_2H_2O_4$,	500
CHAPTER LX.	
LEUCINE AND TYROSINE,	511
CHAPTER LXI.	
OXYMANDELIC ACID, $C_8H_8O_4$,	520
CHAPTER LXII.	
KYNURIC ACID, $C_{20}H_{14}N_2O_6, 2H_2O$,	522
CHAPTER LXIII.	
UROCANINIC ACID, $C_{12}H_{12}N_4O_4$,	524
CHAPTER LXIV.	
LITHURIC ACID, $C_{15}H_{19}NO_9$,	526
CHAPTER LXV.	
DAMALURIC AND DAMOLIC ACID,	528
CHAPTER LXVI.	
UROPHANIC ORGANIC ACIDS,	532

	PAGE
CHAPTER LXVII.	
UROPHANIC ORGANIC BASES AND INDIFFERENT BODIES, . . .	541
CHAPTER LXVIII.	
UROPHANIC SPECIFIC METAMORPHIC PRODUCTS,	546
CHAPTER LXIX.	
UROPHANIC INORGANIC SUBSTANCES,	548
CHAPTER LXX.	
SYSTEMATIC QUALITATIVE ANALYSIS OF URINE AND URINARY SEDIMENTS,	556
CHAPTER LXXI.	
SYSTEMATIC QUALITATIVE ANALYSIS OF URINARY CALCULI, . .	561
CHAPTER LXXII.	
AVERAGE COMPOSITION OF THE NORMAL URINE,	563
ALPHABETICAL INDEX,	565

A TREATISE ON THE PATHOLOGY OF THE URINE.

CHAPTER I. GENERAL CHARACTERS OF URINE.

PHYSICAL CHARACTERS OF URINE.

THE urine which has just been voided by a healthy individual is a clear fluid, of yellow colour, of the temperature of the body, of an odour which is peculiar to it, and is therefore termed *urinous*; it has a saline taste, with an admixture of some bitterness, and reddens blue litmus paper. A short time after the fluid has come to rest in the vessel into which it has been passed, a small, light cloud, of a grayish-white colour, may be observed settling towards the bottom of the vessel. This cloud consists of the mucus and epithelium of the urinary passages.

Clearness and Turbidity of Urine.

Turbidity of urine depends upon the admixture of solid and insoluble substances. The flocculent, small cloud of healthy mucus may be distinguished from other matters by its being easily diffused by agitation, and by its insolubility in nitric acid. So great a turbidity or thickness of the whole mass of urine, however, as after an interval of repose to cause the subsidence of a deposit to the bottom of the vessel or on the side, must be considered as abnormal, and therefore attracts attention. We then proceed to investigate its nature, which, taken together with the other properties of the urine containing the sediment, will often afford great assistance in the inquiry into the seat and cause of the disorder, of which the turbid condition is a symptom.

A

In considering a specimen of urine with regard to its turbidity, great care must be taken in ascertaining whether it was passed in a turbid state, or whether the turbidity and sediment supervened after its emission, or after a lengthened period of rest. The prognosis of many cases is determined by this circumstance, an accurate knowledge of which, not always easily to be acquired, is therefore of practical importance.

Simple clearness of the urine is not evidence that there is nothing wrong in that fluid. Many abnormal substances, the products of disease, are found in clear urine, and many pathological alterations in the quantities of the normal ingredients occur in a limpid fluid.

At the end of this volume are given some tables for discovering the nature of urinary deposits by chemical reagents and the microscope. The appearance in the form of sediments of the separate bodies, normal and abnormal, their reactions and their general behaviour, are given under each body.

Tints of Urine.

The normal amber-yellow colour of urine is due to a colouring matter which enters into the composition of that fluid, and can be separated from it by chemical proceedings. This normal colouring ingredient is capable of generating a series of tints, varying, according to the degree of dilution, from a very faint greenish, through straw-yellow to amber and dark amber. But in many diseases the colour of the urine becomes changed, by the admixture with the ordinary or normal colouring matters of certain pathological ingredients, to yellowish-red, red, reddish-brown, up to deep brown and black. The normal colouring matters of urine are never red or brown, and tints produced by an admixture of these colours cannot be considered as produced by simple concentration of normal colouring matter.

The colour of urine is frequently an exponent of the nature and amount of functional disturbance, and indicates to the physician the direction in which his further examination should proceed. The special indications of the several colouring matters will be discussed under the chapters devoted to their description. Here it may suffice to indicate the general practical conclusions which may be drawn from the different colours as regards the other characters of the urine, and the condition of the organism by which it has been voided.

Pale urine varies from nearly colourless, through a faint greenish tint, up to straw-yellow. It is the urine of early infancy, and is common in adults after the ingestion of large quantities of water or watery fluids. It is mostly neutral, less frequently alkaline, rarely acid. It is common in chlorosis and other anæmic conditions, and then contains a small amount of urea,

and of solids generally. In diabetes, however, the pale colour does not admit of any conclusion as to the amount of solids generally. Practically the general rule holds good, that *as long as a patient secretes this description of urine, he is not affected by any severe illness of a febrile and acute nature.*

Amber-coloured urine is the common urine of health. Its occurrence mostly excludes all diseases of which either the pale or the very highly-coloured urine is a usual symptom.

Highly-coloured urine ranges from a reddish-yellow colour to red, and is of a decidedly acid reaction and high specific gravity, indicating the presence of a large amount of solids, particularly urea. Concentration being the principal and uniform feature of this sort of urine, it is well to bear in mind that it may be produced in four different ways. 1. Either the person voiding such urine has taken very little liquid, and in that case the whole amount of concentrated urine will be very small. 2. Or the water of the blood has been evaporated by the skin in the form of perspiration. 3. The third way in which a concentrated highly-coloured urine may be produced in healthy individuals is by the ingestion into the blood of a large amount or an excess of nutritive nitrogenous matter. It is therefore of frequent occurrence with those who partake of sumptuous meals and drink little water. 4. The fourth mode of formation of this description of urine is by the more rapid disintegration of tissue and waste of matter in febrile diseases. Here the indication is the more valuable, as other symptoms, such as the temperature of the body or the state of the pulse, cannot always be exclusively relied upon as exponents of the intensity of the febrile process. Several of the circumstances enumerated may combine in producing a highly-coloured urine, such as fever and perspiration, or large meals, and violent exercise. In all cases, however, the absolute amount of solids discharged in a given time should be regarded as the prominent indication. The solids must pass through the kidney; the water may be discharged by kidneys, lungs, and skin.

Of the *tints of urine* due to *abnormal substances*, some are strictly *accidental*, viz., produced by introduction into the stomach of articles of food, or beverages, or drugs, the colouring principles of which are absorbed into the blood, and afterwards discharged by the kidneys in the urine. The urine may be very deeply tinted by the colouring principle of coffee, when a tolerably strong infusion of the roasted berry is taken even in moderate quantity. The colouring matters of several drugs, such as the chimaphila or pyrola, hæmatoxylum, senna, rhubarb, enter the urine very readily, and a short time after having been taken into the stomach. Urine coloured by rhubarb is sometimes mistaken for bilious urine. The error can be at once detected by the

addition of liquor ammoniæ, which converts the dark orange into a crimson colour. The addition of mineral acids to urine containing the pigments of either rhubarb or senna changes the brownish or dark-red colour into a bright yellow; while the ordinary colouring matter, if changed at all, is rather darkened by their influence.

Black or blackish urine has several times been observed after the internal use of *creosote*, of *carbolic acid*, and the inunction of *tar* over parts of the body.

The second class of abnormal tints of the urine comprises the *pathological* ones. The range of tints is from lemon-yellow on the one hand, and blue on the other, through all varieties of yellowish-green, apple-green, brownish-green, red (blood colour), through brown, brownish-black, to impenetrable black. The blue colour may be due to *indigo* (formerly described as cyanurine, uroglau-cine, or urocyanine), which is sometimes the product of the decomposition, within or without the bladder, of a peculiar colourless product, *indigogen*, and has been observed in cystitis and albuminuria. Another product of the decomposition of a probably colourless compound, *urrrhodinogen*, is *urrrhodine*, formerly believed to be identical with indigo-red, but differing greatly from it in many features, particularly in that it contains no nitrogen. When the blue pigment occurs in urine containing much yellow colouring matter, it forms a greenish or grass-green; or if the red matter prevail, violet solution, with a variety of modifications, caused by the admixture, in various proportions, of other abnormal, or of normal colouring matter. The effects of *urerythrine*, which is perhaps not always a pathological product, but frequently indicates the presence of serious disease, are a red, rosy, or pink colour of any sediment of urates which may occur in the fluid. The urates seem to have a particular affinity for it. Urerythrine in a blue or lemon-yellow urine would produce changes of colour not dissimilar to those produced by urrhodine, but of less intensity.

The sediments stained with urerythrine, and the sediments which the blue pigments when they occur form with part of their substance, and all sediments whatsoever, must be filtered off before determining the colour of the solution.

A *greenish-yellow* or *greenish-brown* urine indicates the presence of derivatives of the *colouring principles of bile*. There is, however, also a kind of bilious urine, that is, urine which with nitroso-nitric acid yields the reaction characteristic of bile pigments, which is red. Such urine, in chronic cases, of liver disease, gallstone, cancer, and others, alternates with urine of a greenish-brown colour. The more pronounced the jaundice in such cases, the darker is generally the urine.

Dark urine, of brownish or brown porter-like colour, more

rarely of a blackish-grey colour, is the result of severe pathological action in the body, and indicates a rapid disintegration of the red blood corpuscles, the result of which is the appearance in the urine of an abnormal pigment, or several pigments at one time. Sometimes the pigment of dark or black urine is coagulable by heat, thus indicating its being *dissolved cruorine* (hemato-crystalline). It is not rarely accompanied with *hematine*, a product of its decomposition. In other cases such pigments are derivatives of hematine, resembling *cruentine*, *e.g.*, *uro-rubro-hematine*, or decomposed further, *e.g.*, *uro-fuscohematine*. These bodies are most certainly recognised with the aid of the spectroscope.

Odour of Urine.

Healthy urine has a peculiar odour, which rises with the vapour of water after emission. It is almost indestructible by any of the chemical processes usually applied to urine, and therefore accompanies the operator through the whole course of an analysis. The odour is due to the presence of a number of volatile and fixed principles, particularly those which on chemolysis yield the substances to be described as *ur-rhodine*, *omicholine*, *omicholic acid*, *uropittine*, and others. The common modifications of the smell of urine are probably due to the preponderance of one or other of these bodies, and to the admixture of urophanic substances derived directly from the food. Several articles of daily consumption, as coffee, onions, mutton, port wine, or garlic, communicate to urine their peculiar odour. Asparagus communicates to the urine a peculiarly disagreeable odour. Oil of turpentine, when taken into the stomach, or breathed in even a very small quantity, communicates to urine an odour similar to that of violets. The odoriferous principles of saffron and cubebs may be easily distinguished in the urine of persons who have taken them internally.

Taste of Urine.

The taste of urine is a mixture of the tastes of its constituents, of which two, however, characterise it—*urochrome* and *chloride of sodium*; the one imparting a bitterish, disagreeable flavour, the other its saline taste. The phosphatic alkalies are of a cooling, weak saline taste, and so far resemble the *chloride of sodium*. The odorous acids and volatile oil also affect the taste, and the cooling taste of *urea* is perceived in concentrated solutions. The discovery of *diabetes mellitus*, in which disease the taste of the urine is sweet, was formerly made by tasting only.

Chemical Reaction of Urine.

As the chemical reaction of healthy urine is acid, any deviation from this condition becomes at once an anomaly. It has

been ascertained that the neutral or alkaline condition is due not so much to the absolute absence of acid as to its neutralisation by bases; the nature of the latter, and their origin, determine whether the neutral or alkaline state be within the limits of health or a symptom of disease.

The acid reaction of urine is probably the result of the co-operation of a variety of factors, which it is extremely difficult to disentangle. On the whole, it may be said that the acidity is due to the presence of acid salts, such as the phosphates and sulphates of potash and soda, the acid urates, hippurate, extractive acids, such as kryptophanic and paraphanic, and accidentally to free organic acids, such as the oxalic, malic, and tartaric (Buchheim, Wöhler), and their acid salts.

The degree of acidity of healthy and pathological urine can be determined by a volumetrical process, here to be described.

Mode of determining the amount of Acidity in the Urine.

The analysis is performed by a standard solution of caustic soda, graduated so that a given volume corresponds to a certain amount of oxalic acid. With this a known bulk of urine is exactly neutralised, and from the amount of standard solution used we find, by calculation, the amount of oxalic acid which would be equivalent to the amount of free acid actually contained in the urine.

Preparation of the standard solution of Caustic Soda.

This solution is to be graduated so that every cubic centimetre indicates exactly 10 milligrm. of oxalic acid. For this purpose we require a solution of oxalic acid of known strength, which is prepared by dissolving one grm. of dry oxalic acid in so much water that the solution exactly amounts to 100 c.c. Every 10.0 c.c. of this solution contain 0.1 grm. of oxalic acid. This quantity is now measured off, put into a small beaker, and coloured red with tincture of litmus. After being placed upon a piece of white paper, the dilute solution of caustic soda is cautiously added until the red colour has been changed into the original litmus blue. Suppose we have used for effecting this 6 c.c. of the solution of caustic soda, then they would correspond to 1 decigrm. of oxalic acid. We now add to every 600.0 c.c. of the solution of soda 400.0 c.c. of water, and thus obtain 1000 c.c. of standard solution, of which 1.0 c.c. exactly neutralises 10 milligrm. of oxalic acid. If, after the addition of 10.0 c.c. of this solution to 10 c.c. of the solution of oxalic acid reddened by litmus, the blue colour appears, the solution is correct and ready for use.

The fluid applied to the Urine.—To 50 or 100 c.c. of quite fresh urine the standard solution of soda is added in small portions, say $\frac{1}{2}$ c.c. at a time, and after every new addition the fluid is tested by the aid of litmus paper, as the yellow colour of the fluid would not allow the tincture of litmus to show the transition from red to blue, and therefore excludes its use in the manner described for the preparation of the test-fluid. The testing with litmus paper is best effected by placing a drop of the mixture upon neutral blue litmus paper. If, after a time, the spot covered by the drop does not become red any longer, the analysis is completed. To make sure, we may now test for an excess of alkali, and if the latter be found, a fresh analysis, guided by the experience of the first one, will lead to the exact point of neutrality.

The amount of alkalinity of any specimen of urine can be determined by applying to it the solution of oxalic acid described in the foregoing, until an acid reaction of the specimen is obtained.

The neutral state or alkalinity of the urine is the consequence of the admixture of fixed or volatile alkalies. Before speaking of the circumstances, however, under which neutral or alkaline urine may be *discharged* from the bladder, we must advert to the fact that urine, which when passed was acid, may soon become alkaline under the influence of decomposition of urea. This conversion is sometimes effected within an hour after emission. It must be considered as an essentially abnormal feature, because normal urine, though it almost always becomes alkaline during its decomposition, yet does not do so within the first twenty-four hours after its emission.

But the alkaline decomposition of even healthy urine may be favoured by certain circumstances requiring the most scrupulous attention of the practitioner. Urine which is already in a state of alkaline decomposition, when added even in small quantity to healthy urine, will, by means of a ferment, induce and hasten the decomposition of the normal fluid. The vessels, therefore, in which the urine is collected, must be washed and scalded with great care; otherwise the small quantities of decomposing urine adhering to their walls may induce fallacious conditions of the fluid collected.

There are other circumstances which may make the acid urine alkaline in a shorter period than usual. Such are the presence of mucus and pus, which play the part of a ferment in many cases. This may be proved by dividing a specimen of acid urine into two parts, filtering the one immediately, leaving the other as it is, and letting both stand side by side. The filtered urine will often present its original acid reaction, when the portion which has not been filtered is already alkaline.

High temperature and great dilution favour the process of decomposition. A concentrated acid urine of fever, on the contrary, of a specific gravity of 1025, containing much urea, will, when decanted from the deposits, retain for days, if not its entire character, certainly its acid reaction and its ordinary appearance.

Though a certain amount of ammonia, in combination with acids, is present in all healthy urine, yet that quantity is never sufficient to produce an alkaline reaction. When ammonia produces the neutral or alkaline reaction, as it always and exclusively does when the alkalinity has supervened after emission, it is the product of the decomposition of urea into ammonia and carbonic acid.

Having now ascertained the causes of alkaline changes occurring in the urine after emission, we are the better prepared to appreciate the processes by which the urine may become alkaline *before* emission. We have already remarked that this may be effected by volatile or by fixed alkalies; and accordingly alkaline urines may be divided into two great groups. The alkalinity of the first group is always due to the presence of carbonate of ammonium from the decomposition of urea in the urinary passages, particularly the bladder, after its secretion from the kidneys. This may be taken as the general rule; though it is possible, but not proved, that in uræmia, and some other diseases, or when taken internally as a medicine, carbonate of ammonium may be discharged from the blood by the kidneys. Carbonate of ammonium restores the blue colour to reddened litmus paper, but, as it evaporates on drying, its neutralising influence disappears on the dried test-paper, which therefore again becomes red. The fixed alkalies, on the contrary, impart a permanent blue colour to red test-paper. Both descriptions of alkaline urine effervesce with acids, and froth on being shaken, particularly when containing albumen.

The alkaline decomposition of urine in the urinary passages, particularly the bladder, may be referred to a series of causes, all of which have one effect in common, namely, that of preventing the complete emptying of the bladder at one time. A part of the otherwise healthy urine being thus retained longer than it can resist alkaline decomposition under ordinary circumstances, acts as a ferment on all urine subsequently entering the bladder. Upon this point, the experiments and arguments of Snow are quite conclusive. About half a pint of newly-voided urine was put into a glass vessel which terminated at the lower part in a tube of minute calibre, through which it dropped into a glass jar below, at the rate of about twelve drops in a minute, which is about an ounce and a half in an hour, that being not far from the quantity usually passing into the bladder from the ureters. The

vessels were kept near the fire at the temperature of 37.7°C . At the end of six or eight hours, when the urine had all dropped into the lower vessel, this was emptied, all but about thirty drops, and the upper glass, which served as a funnel, again replenished. It was found that the urine in the lower vessel became decomposed generally in about twenty-four hours,—in about the same time, in short, as urine preserved at the same temperature from the beginning of the experiment, the time varying according to the quality of the urine. The mere increase of the contact with air, therefore, did not decompose the urine any quicker. But the thirty drops of decomposed urine left in the lower vessel decomposed every new drop which arrived immediately, so that while the urine was always fresh and acid in the upper vessel, provided this was washed out occasionally, it was always decomposed in the lower one, although the urine, except a small fraction of it, was of the same age in both.

Among the causes which may prevent the complete emptying of the bladder, and produce ammoniacal urine, *foreign bodies* in the bladder claim our attention. They occasionally interrupt the stream of urine before the bladder is emptied; they give rise to the frequent retention of small quantities of urine, because the bladder can seldom contract around them so exactly as completely to expel all urine; and, further, they are mostly porous, and contain urine in their substance. These circumstances lead to ammoniacal decomposition of the urine, in consequence of which most foreign bodies in the bladder become encrusted with earthy phosphates. A catheter, which is left in the urethra and bladder for some days, soon makes the urine ammoniacal and phosphatic by allowing a small quantity of urine to remain in the bladder, even independently of the possibility of its giving access to ferment-forming agents from the atmosphere, or of introducing them by mere adherence to its surface. Enlargement of the prostate and stricture of the urethra, and in rare cases stricture of one or other of the ureters, act in a similar way. Ammoniacal urine is the almost invariable result of weakness, partial or total paralysis of the bladder, more strictly of the detrusor urinæ, such as occurs in paraplegia and spinal diseases and injuries, in the decrepitude of extreme old age, and long-continued comatose conditions in the course of certain diseases, such as typhus.

It is probable that the inflamed condition of the mucous membrane of the bladder, which we mostly observe along with ammoniacal urine, is the *consequence* of this condition of the urine. If ammoniacal urine acts as a caustic upon the epidermis and cutis, causing excoriations and extensive soreness, how much more liable must the mucous membrane of the bladder be to similar affections! The alkaline urine causes positive ulceration

on the mucous membrane in cases of extroversion of the bladder, on the enlarged uterus in cases of prolapse; nothing is then more natural than that the offended surface of the cavity of the bladder should, for its protection, first pour out a large quantity of mucus, and when the cause continue for a length of time, pass into a state of chronic inflammation, with croupy exudations, attended by great suffering.

In very few cases the mere presence of a calculus or foreign body in the bladder causes inflammation of itself; it mostly requires the presence of ammoniacal urine. The symptoms of a calculus not attended by ammoniacal urine are far less severe than those of a concretion accompanied by such urine; and in many cases the presence of a calculus in the bladder is neither observed nor suspected before the appearance of ammoniacal urine and its attendant suffering, which, from the beginning of the phosphatic incrustation, can be shown to have taken place only at a time when the calculus had already attained a considerable size.

There are two conditions more in which the partial retention of urine may cause ammoniacal urine and its consequences. The one is a so-called sacculated bladder, or rupture of the mucous membrane protruding through the muscular coat. The other occurs in insane persons, who have a tendency to retain their excretions as long as possible. When forced to pass water, either by natural necessity or by attendants, they will only allow the passage of a part, retaining another. In one such case, I could frequently observe the urine become ammoniacal fifty hours after the beginning of the paroxysm. This condition is said to be frequent among the inmates of lunatic asylums.

The most efficacious treatment of all cases of ammoniacal urine is the washing out of the bladder with warm salt-water by means of a syringe and double canula. In all cases where the operation has been carried out properly, the urine immediately loses its ammoniacal condition, and in most cases is clear and acid, thus proving the correctness of the above views by demonstration.

In many cases of acute total retention, the urine does not become ammoniacal, but becoming concentrated by the absorption of water, remains acid, but forms deposits of various kinds. These cases have evidently no analogy with those of partial retention, and can therefore not tell against the views here adopted.

Ammoniacal urine is always fetid, pale, and turbid, from the precipitation of phosphate of ammonium and magnesium, and phosphate of calcium. The smell, and the presence of the crystals of ammonio-phosphate of magnesium, easily distinguish it from urine which is only turbid by alkalinity from fixed alkali.

and contains a precipitate of phosphate of calcium, or phosphate of calcium and magnesium. Urine which is alkaline from the presence of dicarbonates (after Vichy water) is mostly clear, the earthy phosphates being soluble in the excess of carbonic acid.

We have thus advanced to the consideration of that group of alkaline urines which impart to red test-paper a permanent blue colour, showing that they are produced by fixed alkalies. When the alkali is present in quantity sufficient only to neutralise the free acid of the urine, then the latter exerts no influence upon any test-paper; it is neutral. But it must be borne in mind that the reaction of healthy urine being acid, neutrality of the fluid in itself denotes alkalinity.

While, on the one hand, the presence of free volatile alkalies in the urine is always pathological, the alkalinity from fixed alkalies on the other hand, though it may be, and in many cases is, of a morbid nature, occurs more frequently within the range of perfect health. Certain descriptions of vegetable food, and a series of acid fruits, make the urine alkaline in a very short time. The salts of many of the organic acids, such as acetates, tartrates, citrates, and malates, are, by the oxydising influence of the chemistry of the body, converted into the carbonates of their respective bases, and being as such discharged with the urine, give it their characteristic reaction. It is for this reason, and some others, that the urine of herbivora is frequently alkaline.

In man this description of alkalinity, which may occur for hours or days, or at a certain time after meals, is of no practical importance. It becomes so, however, when it is the consequence of the use, as medicines, of the caustic alkalies, soda and potash, and of the earths, magnesia and lime, or their carbonates. This artificial disease not unfrequently occurs when patients, to whom alkaline remedies have been prescribed by their medical advisers, continue to take them on their own account for an unreasonable length of time.

I have already stated that the neutral or alkaline condition is of frequent occurrence with the pale urine discharged in anæmic conditions. Of the reason of the alkaline reaction in these cases we can as yet give no satisfactory account. But it seems probable that the depression of the organism in these cases, accompanied as it is by faulty nutrition of the muscular and nervous systems, does not allow of the accomplishment of that chemical process, by the completion of which, in health, acid combinations are discharged from the tissues and blood.

The continuance of the alkalinity of urine from any cause, but particularly from alkaline fermentation and the maladministration of fixed alkalies, for any length of time, is to be considered a serious evil. For the phosphates of magnesium and calcium,

being precipitated, and mixing with the increased amount of mucus, may at any time, and unawares, form a stone, with all its consequences; or the turbid and caustic condition of the urine may give rise to diseased states of the bladder, which it is afterwards frequently a matter of great difficulty to remove.

Amount of Free Acidity in the Urine.

While the amount of *free alkalinity* seems never to have engaged the attention of any inquirer, the amount of free acidity has been estimated repeatedly. Vogel found it equal to from 2 to 4 grains of oxalic acid for 24 hours in a healthy man. This amounts to 0.1 to 0.2 grains per hour. The hourly quantities, however, are subject to considerable variations, dependent upon the time of the day, and these variations are pretty parallel in different individuals examined at one and the same time. The maximum amount of acid is discharged during the night, the minimum during the forenoon, and a quantity intermediate between those of night and morning is secreted in the hours of the afternoon.

Roberts observed the acidity in the urine of a healthy man during nineteen days, and found that it required for neutralisation on an average 14.1 grains of dried carbonate of soda for each 24 hours. Some days were found throughout exhibiting a feeble acidity, the minimum of sodic carbonate required being 5.9 grains; the maximum acidity ever observed in this series was neutralised by 22.39 grains of sodic carbonate. According to Bence Jones, and Roberts, meals, whether of animal, vegetable, or mixed food, depress the acidity of the urine for a time, and in most instances render it actually alkaline. In forty minutes after breakfast there appears, nearly always, a sensible declension of acidity. The urine, however, never becomes actually alkaline, nor ever neutral, so soon. The acidity falls to its lowest in about two-thirds of the observations during the second hour after breakfast; in the last third it does so in the third hour. At the end of the fourth hour the urine usually regains its acidity. The effect of dinner is not perceptible until the second hour afterwards. In the third and fourth hours the urine is mostly alkaline, and at the end of the sixth hour the acid reaction has been restored.

In chronic and acute diseases the amount of free acid in the urine is mostly diminished, increased only in exceptional cases. Frequent or persistent alkalescence of the urine, from fixed alkali, occurs in persons with debilitated frames from *spanæmia*, chlorosis, dyspepsia, chronic vomiting, rheumatism, gout, and chronic pulmonary phthisis. The physiological explanation of these phenomena has not yet been furnished.

Changes on Cooling.

In colour the urine becomes a trifle darker on cooling; its peculiar smell becomes very weak, partly because it does not evaporate any longer with the vapour of water, partly because there is less of it.

The epithelia collect in masses and clouds towards the bottom of the vessel, leaving the supernatant fluid perfectly clear and transparent.

If the urine have been concentrated and dark, it will frequently deposit a reddish crust against the walls of the vessel containing it. This crust, and the pulverulent deposits of urates, which are formed at different stages of the process of cooling, may occur in persons enjoying apparently perfect health.

As a general rule, it may be said that the more coloured a deposit of urates is, the longer time has it required for its formation. A lady having lost her child, was obliged to retain the milk in her breasts. When the painful swelling of the bosom had ceased, she discharged urine, which, on touching the vessel in which it was received, became white like milk, and was brought to me as milk. When only a small quantity was passed, the milk-white condition was at once apparent; the vessel withdrawing a sufficient amount of warmth from the urine to precipitate the urate. But when a larger quantity was passed, the first portion made a precipitate, which was redissolved as the larger portion was added. Ten minutes, however, were sufficient to make the precipitate appear, which consisted of snowy-white urates. Dark-coloured urines mostly throw down the urates after standing during some time. In a case of heart-disease with dropsy, the brownish-red urate only fell after twenty-four hours; in a case of colic, only after twelve hours. In these cases the depression of temperature could not have been the only influence exerted upon the urine, because in each case the urine must have been of the temperature of the air long before the deposit fell.

In some few cases the urine may become alkaline during the process of cooling.

If sediments are discharged with or formed in the urine they subside towards the bottom of the vessel. Among the sediments, besides mucus, the urates, uric acid, and the oxalate of lime are most common. Most other deposits are due to the decomposition of urine, and of the urates in some cases.

CHAPTER II.

QUANTITY OF URINE AND INGREDIENTS.

MODES OF COLLECTING THE URINE.

THE requirements are to collect the whole of the urine without losing any portion, and to collect it in such a manner as to preserve its purity. It is essential to keep all vessels used for the purpose scrupulously clean, and to wash and scald them at least once a day. If practising among the poor, the physician will find it necessary to order that the chamber-vessel be kept covered when not used, in order to protect its contents from the admixture of impurities. In some diseases it is desirable to collect in separate vessels the several portions of urine passed at different times.

In hospitals and other public institutions a convenient form of glass is in use, consisting of a flat body, a turned-up narrow neck, and a mouth fitted to the requirements of the sex. These glasses should have marks engraved upon them indicating 50 c.c. each. The physician, on coming to the bedside, would then be enabled to inform himself by a glance of the total quantity of urine collected; and, if none were lost, of the bulk excreted.

In some hospitals the ancient urinal is still in use; its only advantage over the ordinary vessel is its being made of glass; its shape is less convenient than that of the glasses described above, which admit of the discharge of urine in the recumbent or any other posture,

In many cases the difficulties in the way of collecting the whole of the urine discharged in twenty-four hours are great, and unless a special apparatus be employed, a certain loss is nearly unavoidable.

The matter becomes more embarrassing in cases of severe illness, where, unfortunately, with the importance of the indications to be derived from the quantity and quality of the urine, the obstacles to a complete collection become greater. Patients in a delirious, or unconscious, or paralysed state will retain or pass unconsciously a part or the whole of their renal and alvine excretions. Here we must estimate the losses from known and collected quantities in proportion to time and from the evidence to be derived from inspection.

In this manner we may obtain the nearest possible approach to truthful observation. Unless, however, all the cautions are employed, we would strongly recommend that too nice conclusions should not be based upon such incomplete observations, though they even give to the thinking practitioner points of evidence to which he may append his reflections, and which may be taken into account in forming the prognosis of a case, or in tracing out a plan for therapeutical proceedings.

TOTAL QUANTITY OF URINE DISCHARGED IN A GIVEN TIME.

Any attempt to make a quantitative analysis of the urine for the purposes of physiological or pathological research must be based upon the knowledge of the total amount of urine discharged in a given time. Some authors, though perfectly well aware that in all cases where any approach to accuracy in the determination of the specific gravity is required, an average sample from the urine passed in twenty-four hours must be selected, have yet formed no settled idea of the necessity of knowing the whole amount of urine discharged during the twenty-four hours. It could have been only by losing sight of this point that they recommended the determination of the average density of the urine from the density of a mixture of the urine passed immediately before going to bed, and of that voided on rising in the morning. But of what use is it to know density at all, if from the density we cannot calculate the whole of the solids discharged in a given time? For this we must know the whole amount of urine.

We may either collect the whole bulk of urine passed in twenty-four hours, or in every single hour, or in as many portions of the twenty-four hours as convenient. But it should always be expressed in a value calculated upon the twenty-four hours, or upon every single hour. In many chronic and acute diseases we must collect and analyse the urine for several days in succession, in order to arrive at a correct conclusion upon the average condition.

The amount of urine is best determined by measuring in the graduated urinals; or, if more accuracy is desirable, in high graduated cylinders of a capacity varying from 500 c.c. to 2000 c.c. The large cylinders have marks for every 10 c.c. The small cylinders, which are to serve for measuring the quantities of urine of a shorter period, say one hour, should be divided into single cubic centimetres.

Both descriptions of cylinders should be provided with lips for pouring out their contents.

If it is desirable to know the weight of a certain bulk of urine, without actually weighing it, it is only necessary to multiply the number of cubic centimetres found by measure into the number

expressing the specific gravity ; the result will give the quantity in grammes, thus—

$$\begin{aligned} 1000 \text{ c.c.} \times 1.025 \text{ (spec. gr.)} &= 1025 \text{ grammes.} \\ 250 \text{ c.c.} \times 1.021 \text{ ,,} &= 255.25 \text{ ,,} \end{aligned}$$

Quantity of Urine Discharged in Health.

In valuing the physiological effect of the variations of the discharge of urine, it must always be borne in mind that the water discharged in the urine is only a part of the water excreted by the whole body. According to our best estimates, one-half of all the water ingested into the body goes away by the kidneys ; the other half by the lungs, the skin, and the fæces together.

The quantity of urine discharged in twenty-four hours by healthy adult persons has been determined by various observers. The results of some of their observations, together with the results of my own, are arranged in the following table:—

Table showing the total quantity of Urine discharged in given times by healthy individuals.

Observer.	Subjects.	Found in One Hour.			Found in 24 Hours.		
		Cubic centimetres.			Cubic centimetres.		
		Min.	Med.	Max.	Min.	Med.	Max.
Lecanu . .	Himself,	743	1268	2271
Valentin . .	Himself, medium of three days.	1447	...
Lehmann . .	Himself, under ordinary circumstances.	1057	...
Ditto . . .	Himself, when living irregularly.	909	...	1202
	Well-fed persons who drink much.	60	...	70	1400	...	1600
	Well-fed persons who drink less.	50	...	60	1200	...	1400
Bischoff, Vogel, and others.	For one kilogramme of weight of adult.	...	1	24	...
	For 100 centimetres of length of adult.	...	40	960	...
Thudichum .	A, a man, æt. 28 ; weight, 70 kilos., seventy-six days.	43	81	121	1049	1950	2920
Ditto . . .	B, man, æt. 28 ; weight, 72 kilos., fifty-seven days.	43	71	110	1040	1723	2655
Ditto . . .	One kilogramme of weight of adult man.	...	1.1	26	...
Ditto . . .	100 centimetres of length of adult. [A+B=346 cent.]	...	44	1061	...

Among the influences which determine the quantity of urine, many are inherent in the mode of life, others are entirely independent of any act of the individual. Of the former are the quantity and quality of food and drink, and the amount of perspiration caused by activity.

The ingestion into the system of large quantities of water, tea, coffee, beer, (weak) wine, &c., may in a short time raise the hourly quantity of urine from 60 to 70 c.c. to 300, 600, 700 c.c., and more.

The quantities of water consumed by persons who undergo treatment with mineral waters is sometimes very large. A discharge of urine up to 1000 c.c. per hour is here not an uncommon occurrence.

Abstinence from drink, on the other hand, diminishes the secretion of urine; but this diminution is not exactly in inverse proportion to the increase by drink. The urine does not sink below a certain quantity, even in cases of total abstinence from food and drink. With a dry diet the urine may sink from the medium of 86 c.c. per hour under ordinary diet to as low as 37 c.c.

The temperature of the atmosphere, the amount of moisture diffused in it, and its tension, are influences over which the individual has only partial control. The amount of moisture, therefore, which is exhaled by the lungs and skin—though of course dependent in part on the amount of water present in the blood, on the relative excretory activity of the organs, and on the bodily state of the individual—is partly determined by atmospheric influences.

Certain regular variations in the hourly quantity of urine are produced by the influences of day and night. During the sleep of night only 58 c.c. of urine per hour are excreted; in the morning the medium is 69 c.c.; after dinner, if taken about the middle of the day, or after luncheon, the amount of urine becomes largest—77 c.c., and sinks again in the evening to 73 c.c., when even a late dinner will not influence it so much as might be supposed from the observations after an early dinner. Nothing could better demonstrate the influences of activity and rest upon the quantity of urine than the differences between the secretion during day and night.

Not only is there a greater production of effete matter, during waking and exercise, requiring to be discharged from the blood than during sleep, but also the excretory activity of the kidney is higher, in consequence of the transference of the nervous stimulus, and from the stimulant action of certain substances of aliment, such as coffee, porter, onions, and many other articles of diuretic property. This transferred nervous and direct stimulus may be brought to bear upon the kidneys at any hour

of the day or night, and it is therefore that persons working with either mind or body during the night, discharge as much urine as during the same activity in the daytime. On the other hand, sleep and inactivity in the daytime will diminish the quantity of urine.

To recapitulate: the physiological quantity of urine is dependent, on the one hand, upon the amount of water introduced into the blood, or abstracted from it by other excretory organs; and, on the other hand, upon the excretory activity of the kidneys.

QUANTITY OF URINE DISCHARGED IN DISEASE.

Though in patients all the influences which determine the quantity of urine in health may combine with the influences of the disease, yet as a general rule the consideration of the total quantity of urine in a great number of diseases will convince us that its variation, or a certain mode of variation, forms one of their essential symptoms. In the long run the character of the disease will determine the character of the urine, however the satisfaction of an accidental thirst of the patient may increase it for a time, or however much it may have been diminished by vomiting, diarrhoea, perspiration, or increased pulmonic exhalation.

In the previous remarks we have seen the maximum, medium, and minimum quantities of urine discharged in given times by given weights of individual. This must form the basis of any attempt at judging whether the quantity of urine in a given case of disease is less or more than the same individual would be likely to discharge during health. The only caution necessary is to allow a sufficient margin for accidental variations. If we do so, the practical conclusions arrived at from a consideration of this point are as valuable as any of the most pathognomonic objective symptoms. As an example, we will assume the case of an average adult individual. We know he does not drink a great deal when well, and may therefore put down his medium quantity of urine for twenty-four hours as 1300 c.c. This individual has become ill, and we now ascertain that his urine for twenty-four hours only amounts to 400 c.c. We are at once justified in the conclusion that the disease has brought about a diminution of the bulk of the urine to less than one-third its ordinary medium. Experience teaches us the consequences likely to follow the condition of the system, of which this lessened quantity of urine is a symptom. The symptom therefore has a high diagnostic and prognostic value, as we shall presently more particularly show. An increased amount of urine, on the other hand, to about 2500 or 3000 c.c., in a patient who in health would discharge from 1600 to 1700 c.c., is an evident

excess, which, if not traceable to any special accidental cause, and if permanent, as in diabetes, is the main and principal symptom of the disorder, and therefore the almost exclusive means of its diagnosis.

It is a general experience *that the quantity of the urine is diminished in all acute febrile diseases, viz., in exanthemata, in low gastric fevers and typhus, in rheumatic fevers, in all inflammatory diseases, such as pneumonia, pleuritis, and bronchitis, and in the inflammatory fevers of tropical climates or miasmatic regions. In all these diseases, and in many more, a constant diminution of the quantity of urine is accompanied by, and therefore pathognomonic of, a constant increase in the intensity of the disorder. When the quantity of urine remains very low (below 800 c.c. per day) for any length of time, then we may conclude that the intensity of the disease has not abated. A constant increase in the quantity of the urine, however, is a favourable symptom, and shows that the patient has passed the acme, and that the diseased action is abating. During the period of convalescence the quantity of urine becomes normal, or exceeds in some cases the normal quantity.*

Thus a man, who had measured his urine during health, and found the average to be 1800 c.c. in 24 hours, became the subject of typhoid fever. During the first three days of the illness the total quantity of urine fell gradually to 200 c.c. in 24 hours; it rose during the next five days regularly up to the normal 1800 c.c., exceeded the amount soon up to 2200 c.c., and then returned gradually to the usual average quantity.

When a disease, acute or chronic, takes a fatal turn, the quantity of urine becomes frequently very low, or remains in a fluctuating low state. This is the case in all diseases ending with or by exhaustion. In cases, however, the fatal termination of which is due to a more sudden interference with the powers of the nervous system, or with the mechanical action of the lungs and heart, the quantity of the urine is not usually very much diminished.

The quantity of urine is materially diminished in dropsical diseases, with or without diseased kidneys. Common practice has made the amount of urine discharged by such patients the index of their improvement or otherwise, and has made a small quantity of urine, in cases in which the cause of the disorder is not the kidney itself, an indication for the administration of diuretics.

The quantity of the urine is materially increased in those diseases which we commonly term diabetes. In these cases, however, as in cases of diseased kidneys, it is necessary to give particular attention to the quality of the urine at the same time, when the distinctions between hydruria, diabetes insipidus, and diabetes mellitus will become evident.

SOLIDS AND WATER—SPECIFIC GRAVITY.

The direct way of determining the amount of solids contained in a given quantity of urine is by the evaporation of the water. This is best done under the receiver of the air-pump, care being taken not to make the urine boil, in order to prevent loss from the bursting of the bubbles evolved. By placing into the receiver any body capable of freely absorbing water, such as sulphuric acid or quicklime, the vapour may be absorbed as soon as evolved, and in this way a vacuum for air and vapour may be kept up, under the influence of which the urine will rapidly get dry.

The vessel in which the urine is exposed should be rather flat, so as to give the largest possible surface for evaporation, and should be provided with ground edges, so that it may be closely covered with a glass disc. This caution is required in order to prevent the residue from absorbing water from the air, on being transferred from the receiver to the scales for weighing. The weight is now determined in the closed box of the chemical scales, the air surrounding which is kept dry by the presence of sulphuric acid and chloride of calcium. Then the vessel with the residue is again removed to the receiver of the air-pump; after it has been exposed for a time to the evaporating influence, the covered vessel is again weighed; and if it have lost nothing during the last exposure, the residue is considered to be perfectly dry. Of course, if it have lost in weight between two weighings, it must yet be brought repeatedly into the vacuum, until the weight remains stationary.

This process is one of extreme difficulty and great expense of time; but it is the only one which gives accurate results. Less accurate is the following method, in which the evaporation of the water is effected by the assistance of heat. The objection to the application of heat in this process is, that it decomposes a certain amount of urea, which is volatilised in the form of ammonia and carbonic acid. This objection is so well founded, that if the products of evaporation are caught in a cooler, it will almost always be possible to find traces of ammonia in the condensed distillate. This ammonia, of course, must not be confounded with the ammonia proper of the urine. By always keeping the urine acid during evaporation, the decomposition of urea may be limited to a minimum; but alkalinity of the urine will favour the destruction of urea during the application of heat. However, where no air-pump is at hand, and where ordinary results only are required, the method now to be described is still of considerable use.

The operator pours about 12 or 15 grammes of urine by weight

or measure into a porcelain or platinum capsule, which, with a well-closing cover, has been counterpoised beforehand. It is then fitted into the ring of the water bath, so that the greater part of its outer surface is surrounded by the hot water.

If the solids only are to be determined, the best plan is to take a flat, small evaporating dish for the operation.

When the urine has evaporated to an apparently dry residue, the capsule must be transferred to an air-bath,—a box of copper, with double walls and a sliding door of glass in front. The substances to be dried are placed upon a sieve of perforated copper or gauze, which is placed in the interior of the box in such a manner as to prevent any heat conducted by the metal, particularly the bottom, from reaching the substances. Thus they can only be affected by the hot air, the temperature of which is ascertained by a thermometer, placed with its bulb inside the box.

The capsule being in the air-bath, the air is now heated with a spirit or gas-lamp, under the box, to 110° C., and is kept at that temperature from half an hour to an hour. Being ready for weighing, the capsule is covered, and allowed to cool over sulphuric acid.

After the weight of the capsule and contents has been ascertained, it is again exposed to the temperature of 110° C., and if, after some time, a second weighing does not show a further loss, the residue may be considered as dry.

We now find by easy calculation the amount of water evaporated, and the amount of solids contained in a given quantity of urine. If the total quantity of urine discharged in twenty-four hours be known, the total of solids discharged therewith is readily found: for the quantity of urine (u) taken for evaporation stands to residue (r) found, in the same proportion as the total quantity of urine (U) discharged in twenty-four hours stands to the (R) solids dissolved in it.

$$u : r = U : x; \text{ hence } x = \frac{U r}{u} = R.$$

For example, let the quantity of urine experimented on be 10 grammes, the quantity of solid residue in it 0.23 grammes, the total quantity of urine discharged 1000 grammes, then

$$\frac{0.23 \times 1000}{10} = 23 \text{ grammes,}$$

the total quantity of solids dissolved in the urine.

As the urine is a solution of several substances in water, their amount, viz., the amount of solids contained in any given quantity, may be ascertained by finding the specific gravity; for the

specific gravity of any watery solution is higher than pure water in proportion to the amount of solids dissolved, the solids in solution giving up their own individual specific gravity, and influencing the specific weight of the solution by their absolute weight only. This is proved by the fact already mentioned, viz., that the absolute weight of a given bulk of urine may be found by multiplying the bulk, as expressed in cubic centimetres, by the figure expressing the specific gravity.

The best mode of discovering the specific gravity of the urine is to compare the weight of a certain bulk with the weight of an equal bulk of water of the same temperature. For this purpose any little flask of convenient size may be used; but best of all vessels is the pycnometer, a small glass bottle, the elongated ground in stopper of which is a capillary tube. The advantages thereby obtained are, that no air can be inclosed in the bottle, being displaced by the rising water when the stopper sinks into the full bottle; and that the bottle can be accurately filled with the same bulk of fluid every time.

The weight of the specific gravity bottle, and of the water required to fill it, being each ascertained, are permanently noted down. The weight of the urine required to fill the bottle is then ascertained. Then the weight of water : weight of urine = specific gravity of water : specific gravity of urine. Or, the specific gravity of water being 1,

$$\frac{\text{weight of urine}}{\text{weight of water}} = \text{spec. grav. of urine.}$$

Ex. A bottle held 50 grammes of water, and 51·2 grammes of urine.

$$\frac{51\cdot2}{50} = 1\cdot024 \text{ spec. grav. of urine;}$$

Or, $50 : 51\cdot2 = 1 : x$

$$x = \frac{51\cdot2}{50} = 1\cdot024.$$

Another and more convenient mode of finding the specific gravity of the urine is founded on the fact of immersed solids displacing a bulk equal to their own. For this purpose a solid glass ball is used, the loss of which, when weighed in water, is known, and permanently recorded. It is then weighed while immersed in urine, and its loss, as compared with its weight in air, is ascertained. Then its loss when weighed in the urine, divided by its loss when weighed in water, will be the specific gravity required.

Ex. A glass ball lost 50.0 grammes when weighed in water, and 51.2 when weighed in urine.

$$\frac{51.2}{50.0} = 1.024.$$

Though the two methods last described do not require so much time and weighing as the first two methods, still they are sufficiently troublesome to exclude them from general application. The only method of ascertaining the specific gravity of urine for the practical purposes of diagnosis and prognosis at the bedside, is the use of the gravimeter, or areometer, which, when destined to be used for the urine only, should be called urogravimeter, but has been wrongly termed urinometer. The mode of action of this instrument depends upon the fact of solids of a given weight sinking deeper in light than in heavy fluids.

The urogravimeters are generally made of glass, and consequently are apt to break; but their advantages are, cheapness, and the property of the glass to compensate by expansion or dilatation for any diminution of the density of the urine by a higher temperature between 15.5° and 26.6° C.

Ordinary gravimeters only admit of reading half division of degrees of specific gravity so-called; and if the instrument is small, these divisions come so near together that it is sometimes impossible to say which division corresponds to the proper level of the fluid. In order, therefore, to obtain more accuracy, by having more divisions and by having them farther apart, it is advisable to divide the scale upon two gravimeters, of which the one may range from 0 to 18, the other from 18 to 36, which is beyond the density of almost any urine. In this manner we double the length of the scale, and may now mark and read quarters of divisions.

In taking the specific gravity of urine it is necessary to determine its temperature by the aid of a thermometer; [some specific gravity bottles are provided with a thermometer, the bulb of which performs the function of stopper] the temperature should be 10° C., being the average temperature to which most gravimeters are adapted; or if it is not of this degree naturally, it must be brought to it by suitable means.

From the specific gravity so found, the quantity of solid matters present in the urine is calculated with the aid of a formula, which must be ascertained from the results of the more accurate methods we have described. Among the many formulæ so given two only appear to me sufficiently well proved to advise their adoption in practice. The first and most convenient formula is that of Trapp:—

d = difference between 1000 and specific gravity of urine.

Formula: $d \times 2 = x$ (total of solids in 1000 parts); or

Rule: To find the amount of solids in any given bulk of urine, double the last two figures of the number expressing the specific gravity: the product shows the number of parts of solids contained in any thousand parts of urine. This formula seems to be particularly applicable to urine of a low specific gravity, from 1000 to 1018, being the range of the first gravimeter.

The second formula, which is best suited for urine of a higher specific gravity, from 1018 to 1036, the range of the second gravimeter, is that of Christison. It is: $d \times 2.33 = x$, and means, in other words: multiply the last two figures of the number expressing the specific gravity by 2.33, and the result is the total of parts of solids in any 1000 parts of urine. The results of the calculations with this formula are embodied in the following table:—

Sp. gr.	Solids in 1000 parts.	Sp. gr.	Solids in 1000 parts.	Sp. gr.	Solids in 1000 parts.
1018	41.94	1026	60.58	1034	79.22
1019	44.27	1027	62.91	1035	81.55
1020	46.60	1028	65.24	1036	83.88
1021	48.93	1029	67.57	1037	86.21
1022	51.26	1030	69.90	1038	88.54
1023	53.59	1031	72.23	1039	90.87
1024	55.92	1032	74.56	1040	93.20
1025	58.25	1033	76.89		

Having in this way found the number of parts of solids in any thousand parts of urine, we may easily calculate the whole amount of solids secreted with the urine in twenty-four hours, if we have ascertained the quantity so secreted. And as it is necessary to know the weight of the whole bulk of urine for finding the weight of the total of solids contained in it, the weight is first ascertained from the specific gravity, by multiplying the figure expressive of the bulk by the figure expressive of the specific gravity. By the specific gravity, therefore, we may obtain two kinds of information: (1) the weight of a given bulk of urine; (2) the amount of solids contained in urine.

Ex. A patient passed in twenty-four hours 1250 grammes of urine of the specific gravity 1020. 1000 grammes of this urine hold dissolved 46.6 grammes of solids, then

$$1000 \text{ grammes} : 46.6 \text{ gr.} = 1250 \text{ gr.} : x$$

$$x = 58.25 \text{ gr.}$$

Ex. A patient passed on the average 60 c.c. of urine per hour, of the specific gravity 1012. 1000 parts of this urine hold

dissolved 24 parts of solids. What is the amount of solids in 60 c.c.?

$$1000 : 24 = 60 : x$$

$$x = 1.44 \text{ grammes.}$$

In calculating the solids from the specific gravity, we are liable to commit an error amounting to one-tenth or one-seventh of the solids actually contained in average healthy urine; and the error may be either above or below the amount actually contained. In concentrated urines and the urine of disease, however, the difference between the calculation from the specific gravity and the real quantity may amount to one-fifth, or even one-fourth of the solids actually contained. It is therefore possible to find 30 or 50 parts of solids in a number of parts of urine which positively only contain 40. This is the worst case; but it shows that to slight fluctuations in the specific gravity, and the amount of solids calculated therefrom, we can in practice accord no importance. If we find, for example, that an individual discharges on an average 55 grammes of solids per twenty-four hours in his urine, a rise to 60 grammes, or a fall to 50 grammes, per twenty-four hours, cannot be considered abnormal, because it may be that the difference is only due to the error of calculation to which the method is subject; and the individual may actually have discharged his 55 grammes, or any number of grammes between the 50 or 60. If we find, however, from the specific gravity, that a person who on the average discharged 60 grammes per twenty-four hours, discharges only 30 grammes, we are perfectly justified in drawing the conclusion that this person voids a much smaller amount of solids in the urine than he did before; and though we cannot positively say whether he actually discharges 30, or 25, or 35 grammes, yet 30, 25, or 35 are so greatly different from 50, 55, or 60 grammes, that the diminution cannot be due to the faults of the method, and may with propriety be used as evidence for the diagnosis, or as an indication for the treatment of the case.

Many authors coincide in making 1020 the average specific gravity of urine, and if of this urine from 1400 to 1600 grammes are discharged during twenty-four hours, the gravimetrical method gives a mean amount of solids of from 55 to 60 grammes for twenty-four hours.

100 kilogrammes of individual discharge on an average 4.1 grammes of solids per hour, 100 centimetres discharge 1.5 grammes.

The amount of nourishment acquired from ingested food, the intensity of the destruction of matter serving the purposes of life, as found by the comparison of times and quantities, the activity of the secreting organs themselves—all these factors are summed

up in the total quantity of solids contained in the urine. It is natural then that *in disease generally, where little solid food is being taken, the amount of solids sinks from the daily 60 to 50 and 40 grammes*, and even then is made up less of the produce of the destruction of fresh nourishment in the blood and muscles than of disintegrated tissues and their interstitial juices; in other words, is formed mostly at the expense of the body, as is entirely the case in simple inanition. A patient lives on his own albumen and fat partly during his illness, as hybernating animals do during the winter. The consequence is loss of weight or emaciation.

I have now spoken of disease generally; and the remarks made of course apply to the two great classes of disease, acute and chronic, with equal force. But the fluctuations in the amount of solids occurring in both are of a very different prognostic value; for in chronic disease, with a limited amount of solids, a rise in their amount is, as a general rule, a forerunner of considerable and mostly lasting improvement, and indicates that the body is actively employed in renewing the material of the organs and rectifying their functions. To this rule diabetes mellitus alone forms an exception, where a rise in the amount of solids indicates an exacerbation; and, in this respect, diabetes forms the transition from chronic to acute disease, in which, on the whole, a rise in the amount of solids in the urine during the acme is an unfavourable symptom, indicating an excessive disintegration of the tissues and juices of the body, which must necessarily lead to exhaustion of the material substrata of life. Under all circumstances, a constant and gradual decrease of the amount of solids is as unfavourable a symptom as the decrease of the total quantity of urine discharged, because it indicates the decay of life, and a probable fatal termination of the case.

The indications of the solids appear more varied as soon as they are considered with relation to the amount of other excreta. First, as regards the amount of water by which they are accompanied in the urine, four distinct classes of cases must be borne in mind. If a very small amount of solids is contained in a similar amount of water, we may conclude upon a corresponding amount of anæmia in the individual, always provided that disease of the kidney be not present. In the latter case a small amount of solids indicates the retention of part of them, which may probably end in uræmia.

If a small amount of solids is contained in a larger or large amount of water, it may possibly be the consequence of excess of drink of some kind. Many cases of hysteria, of anæmia with hysterical symptoms, are accompanied by this description of urine. It is the essential symptom of a decided improvement in many cases of hydræmia and dropsy; and when it occurs in

a patient with no particular cause to account for it, it has properly been termed *hydruria*. The urine in *hydruria* may amount to between 2 and 3 litres, and show specific gravities varying between 1005 and 1012, indicating an excretion of solids not exceeding 40 grammes in 24 hours.

When the amount of solids becomes larger, but still remains below the standard of health, and the amount of water is at the same time diminished, in other words, in diseases with a small amount of urine of high specific gravity, the acuteness of the pathological process is clearly indicated. Beginning with the physiological excessive perspiration, there are many pathological conditions, as the sweat of fever, thirst, starvation, diarrhoea, and fever of essential or symptomatic nature, of which this condition of urine is a regular symptom.

In the fourth class of cases both the solids and the water of the urine are present in excess. They form a special and specific class of diseases, to which the generic name of diabetes has been given. The genus has, however, only two species, of which the one is distinguished by the presence in the urine of sugar, and therefore goes by the name of diabetes mellitus; the other subdivision comprises cases where, in a large amount of water, the increased amount of solids is made up of other solids than sugar, termed diabetes insipidus. In both species of diabetes the wear of the body is considerable, and either at intervals or throughout the course of the disorder, surpasses the amount of nutriment taken in. Diabetes mellitus, from its chemical interest, and the facility with which it may be artificially produced in animals, has been favoured with more attention of late than diabetes insipidus, a disease with which perhaps many difficult cases of hysterical anæmia and intractable ailments will have to be classed. If the total quantity of urine amounts to more than 3000 c.c. per day, and if the specific gravity shows an excessive amount of solids, ranging from the normal 60 grammes up to 130 grammes, or even more, giving on an average about 80 grammes per day, we may then with perfect safety ascribe the excessive destruction of the constituents of the body to this excessive secretion, and place to its account a number of symptoms usually following in its train, such as the pallor and the headache of anæmia, vertigo, the tenderness of certain dorsal vertebræ on pressure, spasms in the muscles of various parts of the body, loss of appetite, loss of weight, and emaciation.

We have now considered in its bearings the observation of the amount of solids in relation to the water in which they are contained; it only remains to draw attention to the important conclusions to be derived from comparing the amount of solids secreted by the kidneys with the excreta of the skin, lungs, and

bowels. In many cases of dropsy the bowels will spontaneously compensate partly for a diminished discharge of urine ; and it is, in fact, by this vicarious discharge that drastic purgatives are of service in disease of the kidneys. The skin will eliminate urea in cholera in such quantities that it may be collected by washing and crystallisation, and its amount may even be determined. The lungs will, perhaps, in many cases take on increased action, and discharge not only water, but also carbonic acid, to compensate for a diminished secretion by the kidneys and skin. A diminution in the amount of solids in the urine requires therefore to be checked by the amount of vicarious discharges. And should we be able to determine at the same time the amount of the ingested nutritive matters, we should at once be in a position to balance the income and expenditure of the body, and thereby not only to foresee the probable result, but also to be in possession of the indication for part of our treatment.

CHAPTER III.

UREA.— $\text{CH}_4\text{N}_2\text{O}$.

HISTORY AND LITERATURE.

UREA was discovered by Boerhaave before 1720. From the English translation of his "Method of Chemistry," by Shaw and Chambers, Part III., "Processes upon Animals," p. 193, I quote the following paragraph, as it is the best vindication for that great physician of the merit of this important discovery:—

"PROCESS LXXXVII,

*"Showing that recent urine will crystallise by inspissation,
and afford an essential salt.*

"1. *The Process.*—Evaporate a large quantity of the recent urine of a healthy man to the consistence of a syrup, with one continued degree of heat; separate the oil from it by the filter, and afterwards put it into a close vessel, and set it in a cool cellar for the space of one year; it will shoot into a thick, brown, saline glebe or crust, at the distance of an inch or two from the bottom of the vessel; then carefully pour off all the liquor that floats above, take out the mass of saline crystals, and lay the matter at the bottom thereof aside for phosphorus. These crystals, which are of a peculiar nature, being dissolved in pure warm water, filtered, and evaporated to a pellicle, and set again to shoot in the cold, will again run into crystals *sui generis*, or a white purified salt, of a nature different from all other salts, and become the purer the oftener the process is repeated; so that it may justly be called *the essential salt of urine*, or of the human body.

"2. *The Nature of the Production.*—It may indeed be objected that this salt is not obtained but by suffering the urine to putrify, which is true; nor is there any other way yet known of producing it. Neither will the addition of oil of vitriol, or any other acid, prevent its putrefaction, so strongly is it inclined thereto. It cannot, however, be said that this is the common or sea-salt, which will evidently appear upon the comparison; this

being totally volatile at the fire, whereas sea-salt remains fixed in the strongest heat. Neither has it the properties of borax, nitre, sal-gem, sal-ammoniac, &c., but is really a salt *sui generis*, and not to be matched by any other salt in nature. The process for making it is indeed tedious and laborious; and it cost me no small pains to discover in what manner the salt did really exist in the human body. To do it with the greater advantage, I have evaporated more than two hundredweight of recent urine, and treated it in the method already delivered, by which means I came to a knowledge of the essential salt of the human body; and upon trial find that it is of a wonderful diuretic and emmenagogic virtue, yet without any sharpness at all, being neither alkaline nor acid.

"This salt cannot be so easily obtained from the blood or bile, by reason of their grossness, tenacity, and the large quantity of oil wherewith they abound; but readily enough from urine, which is, as it were, the *lixivium* of the blood."

The objection which Boerhaave himself raises to his process, we now know to be unfounded. Urine concentrated to the consistence of a syrup, and enclosed in a stoppered vessel, does not perceptibly putrefy, in our present sense of the word, even if kept for several years. It can therefore not be doubted that Boerhaave obtained urea in the most direct manner, and recognised it as a peculiar organic substance, the essential salt of the human body, and described all its properties as far as the means at the command of the science of his day permitted.

This great discovery, however, like Proust's discovery of the products of decomposition of the colouring matters of urine, lay dormant for more than fifty years. When it was again made, it was less perfect and less direct, but announced with an *eclat* sufficient to give it notoriety, and secure a permanent registration in the annals of science. It was Rouelle, the younger, who in 1773 conceived the idea of extracting, with spirit of wine, the syrup obtained by the evaporation of urine, commonly termed "the saponaceous matter." He found the extract crystallisable, but believed it to contain hydrochloric acid as an essential ingredient. He failed in what Boerhaave had succeeded, the separation of urea from chloride of sodium. But having recognised the existence of that peculiar crystallised extract in the urine of man, he extended his researches to animals, and found the urine of the horse, cow, and camel to be impregnated with the same substance as that of man. Having extracted the principal crystalline ingredient, he left the brown syrup, insoluble in spirit, under the name of "extractive," to the skill or despair of subsequent inquirers.

History tells us that Margraff noticed urea. Scheele (Op. II. 207) noticed the nitrate without elucidating its nature.

Cruikshank ("Experim. on Urine," p. 438, *et seq.* of Rollo's "Treatise on Diabetes Mellitus," 1798) discovered the nitrate, and accurately described many of its properties. He declared it to be an animal acid hitherto unknown, and whose basis existed in the extractive matter. This basis was in the following year separated by Fourcroy and Vauquelin, recognised to be the crystallised substance of Rouelle, and termed urea ("Syst. d. Connais. Chim." 10, 153). Berzelius was the first to obtain it quite colourless by means of oxalic acid, and Prout ultimately obtained it quite pure, and established its composition ("Ann. Chim." 10, 369). The nature of the change which it undergoes during the putrefaction of urine was pointed out by Proust in a memoir on the urine in the "Ann. Chim." 1800, which we have particularly noticed under the heading of urochrome. The same putrefactive process was investigated by Fourcroy and Vauquelin, and subsequently by Thénard, neither of whom, however, made any important additions to the observations of Proust.

After its decomposition to cyanic acid and ammonia had been proved, Wöhler produced it artificially by evaporating a mixture of cyanic acid and ammonia. For this artificial preparation of urea Liebig subsequently gave a formula.

Occurrence and Modes of Formation.

Urea is a never-failing ingredient of the urine of man and mammalia, and in smaller quantities of birds and reptiles. As it is the principal product of the metamorphosis of nitrogenised food, it occurs more copiously in the urine of carnivorous than of herbivorous animals. Its regular occurrence in healthy blood, and the inability of chemists to find the smallest traces of it in the juice of flesh, speak in favour of the opinion that it is produced within the blood, and only secreted, but not made, by the kidneys. It is also an occasional, but perhaps not a regular, ingredient of the sweat of man. When the action of the kidneys is partially or totally suspended, urea accumulates in the blood, and accompanies in larger quantities than in health the sweat secreted under these circumstances, and passes with the abnormally effused serum into the cellular tissue and the cavities of the body. The sweat and dropsical fluids of patients labouring under disease of the kidneys are therefore richer in urea than the sweat of healthy persons, or the serum effused in cases of dropsy unconnected with kidney disease (Rayer and Guibourt, "Gaz. Méd. de Paris," 1836, Juill.; Müller's "Archiv." 1837, p. 440). In cholera the secretion of urine is suppressed for a time, and consequently the blood becomes richer in urea than usual, and a considerable amount of urea is found in the perspiration which collects on the skin, and in the cerebro-spinal fluid

(Marchand, "Journ. für Pract. Chem." 11 (1837), 449). Millon believes to have found urea in the vitreous and aqueous humors of the eye ("Compt. Rend." 26, 121). Some observers also claim to have found urea in the milk, blister-serum, and the copious evacuations produced by elaterium of persons suffering from kidney disease. But their proceedings and tests are not sufficiently methodical to be admitted without questioning. It was formerly believed that the crystallisation in octahedra of common salt, which ordinarily crystallises in cubes, was a sure sign of the presence of urea; and Marchand ("Journ. der Pract. Chem." 1838, p. 500), observing this peculiar form of crystals in the extract of the blood of cows and calves, pronounced it to be evidence of the presence of urea in it. But we now know that this occurrence may be the result of the presence of many matters besides urea, and may frequently happen without the intervention of any urea, and may, moreover, fail in the presence of urea. It has, therefore, no diagnostic value whatever, and all statements concerning the occurrence of urea based upon it must be considered as erroneous.

Urea was found in the liquor amnii by Wöhler ("Ann. Chem." 58, 98), but is certainly present in exceptional cases only, as I have shown in an essay, to which the University of Heidelberg awarded a prize medal.

The diffusion and presence in various parts of the organism of urea have been elaborately inquired into by two French physicians (Gallois, "Journ. de Pharm. et de Chim." (3), 32, 64; and Picard, "Thèse," Strasbourg, 1856). But their methods of investigation leave much to be desired, and have in no case been controlled by final or elementary analysis of the products obtained.

When a mixture of cyanic acid and ammonia is evaporated, crystals of urea are obtained ($C_2N_2O + 2NH_3 + H_2O = 2(CH_4N_2O)$). The same combination takes place when a metallic cyanate, such as cyanate of potash and a salt of ammonia, such as the sulphate, are mixed. A double decomposition then ensues, from which sulphate of potash and cyanate of ammonia or urea result.

When carbonate of ammonia enclosed in glass tubes sealed at both ends is heated to 150° for some hours, a minute quantity of urea also forms, and after resolution of the contents of the tube in water, and evaporation of the carbonate, gives a characteristic precipitate with nitric acid. Other observers have found that the carbamate of ammonia behaves similarly to the carbonate.

Urea is a frequent product of reactions instituted with several ingredients of urine, such as creatine, uric acid, and with some products of their decomposition, such as allantoin and alloxane. It is observed to form amongst the products of the dry distillation of uric acid, and of the oxydation of oxamide, when passed through a red-hot iron tube or heated with oxyde of mercury.

Modes of extracting Urea from Urine and other Animal Fluids.

1. A quantity of caustic baryta, in the proportion of 5 grms. to the litre, is dissolved in urine by means of a little sieve suspended near its surface. A saturated solution or nitrate of baryta is then added, until a precipitate is not any longer produced. The fluid is then filtered from the precipitate, neutralised with nitric acid, and evaporated to dryness on the water-bath; the residue is extracted with alcohol; the alcoholic extract is again evaporated, and exhausted a second time with absolute alcohol. This last solution contains the urea very pure, so that on evaporation and standing, it crystallises out in colourless needles.

2. The presence of albumen in urine or other animal fluids requires a modification of this process. It is not advisable to remove the albumen by boiling whenever it is present in considerable quantity. For albumen, on passing into an insoluble condition, encloses in its substance a certain amount of urea, which, when only little urea is present, as in blood, may amount to the entire quantity present, and cannot afterwards be separated from it without great loss of time and trouble. The albuminous fluid, therefore, particularly blood, should be at once mixed with absolute alcohol, the precipitate exhausted with spirit, and the united extracts evaporated. From these concentrated solutions all that baryta can precipitate is removed; the filtrates, after neutralisation and even acidification with a little acetic acid, are evaporated to dryness, extracted with absolute alcohol, and the extract evaporated. Any urea will be obtained in a crystalline state. It should be crystallised in needles, be entirely volatilised after fusion from heated platinum, without blackening, and its concentrated watery solution should yield the characteristic reactions with nitric and oxalic acids, and nitrate of mercury. It may then be dried and weighed, or its quantity determined volumetrically.

3. The urine is evaporated at a gentle heat and reduced to a clear extract, in the manner described under urochrome. It is then mixed with an equal volume of nitric acid. If the mixture is allowed to get hot, a considerable effervescence, accompanied by some loss of urea, is observed; but the crystals subsequently obtained are much less coloured than when the mixing has been effected gradually, and with the aid of refrigeration. The crystals are placed upon bricks, and, when dry, dissolved in boiling water, and decolourised by animal charcoal. The solution is then neutralised by carbonate of baryta or potash, and concentrated until it crystallises. The mother liquor, containing nearly all the urea, is decanted from the crystals of nitrate of baryta or potash, evaporated to dryness, and extracted with alcohol. The solution or evaporation will furnish pure urea.

4. The clear extract may be mixed with a concentrated solution of oxalic acid, and the crystals formed, which are but little coloured, entirely decolourised by charcoal. The solution is decomposed by carbonate of lime in the state of powder, and the filtrate, on evaporation, yields pure urea, which by repeated crystallisation can be obtained so pure that the employment of alcohol becomes unnecessary.

Mode of obtaining Urea artificially.

Mix intimately 28 parts of dry ferrocyanide of potassium with 14 parts of manganese, and heat on an iron sheet plate over an open fire, until the mixture ignites and is slowly burned through. Extract the blackish-grey mass which remains with cold water; add to the filtered liquid $20\frac{1}{2}$ parts of dry sulphate of ammonia; let it stand, in order that the sulphate of soda may crystallise; separate the crystals from the solution containing urea; evaporate the latter to dryness, and extract with alcohol, which leaves the rest of the sulphates undissolved, and, on evaporation, gives perfectly pure and white urea.

Physical Properties.

Urea crystallises in quadratic prisms, from a solution in water with a rectangular terminal plane, from a solution in alcohol with octahedral planes. The long four-sided prism becomes six-sided when two of its diagonal edges are replaced by two vertical planes of a secondary prism, and eight-sided when the other two edges are also replaced by the secondary prism. One or two octahedral planes may predominate, and crystals obtained from urine, and seen by the microscope, may consequently appear to be terminated by one or two inclined planes only. The crystals polarise with a gentle blue colour. Their microscopic characters, unaccompanied by characteristic chemical tests, cannot be relied upon for diagnosis.

Chemical Properties.

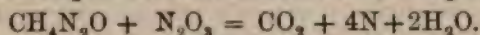
Urea is colourless, of a bitterish, cooling taste, like saltpetre, which has been mentioned as being in part the taste of urine. When dry, it is not changed by exposure to the air, and then attracts very little moisture. A pure solution in water, even when dilute, does not undergo any spontaneous chemical change. It has no reaction on vegetable pigments. It is soluble in its own weight of water of 15° C., in five parts of alcohol, of 0.816 specific gravity, at the ordinary temperature of the air, and in its own weight of boiling alcohol. It is almost insoluble in ether, and quite insoluble in oil of turpentine.

Formula: $\text{C H}_4\text{N}_2\text{O}$.

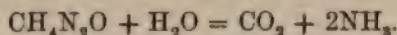
Decompositions.—Urea may be decomposed by the influence

of heat, acids, alkalies, salts, putrid animal matter, and yeast. When exposed to a temperature of 120° C. it fuses, but the temperature being raised a few degrees, ammonia and carbonate of ammonia are evolved, leaving ammeline, amorphous white matter, then cyanate of ammonia, cyanuric acid and its derivatives, until at last the residue chars, and at a red heat burns without leaving any residue.

Nitrous acid, and nitric acid coloured red by the presence of the former, decompose urea into carbonic acid, nitrogen, and water.



The same decomposition is produced by a solution in nitric acid of the nitrite of the suboxide of mercury. This decomposition is employed in the quantitative analysis of Millon ("Compt. Rend." 26, 119). Urea, when fused with potash, or treated with concentrated sulphuric acid, is transformed into carbonic acid and ammonia,



The quantitative analyses of Heintz ("Poggend. Ann." 66, 114; 68, 393) and of Ragsky ("Ann. Chem." 54, 29) are based upon this influence of sulphuric acid upon urea.

The same decomposition of urea may be produced by the influence of heat in the presence of water. A solution of urea, when enclosed in a glass tube, by the assistance of the blow-pipe, and kept for several hours in an oil-bath or well-regulated air-bath, at a temperature of 140° C. will decompose in this manner; and if a sufficient amount of hydrate of baryta be present in the tube, the decomposition at a temperature of from 210° C. to 240° C. will be accelerated by the alkali, and the carbonic acid evolved will be immediately fixed by the baryta. From the quantity of carbonate of baryta so produced, we may ascertain the quantity of urea present in the fluid before the experiment. This is the process employed in the method of Bunsen ("Ann. Chem." 65, 375).

The decomposition of urea into carbonic acid and ammonia is further the result of true fermentation, induced by ferments, such as yeast, or decomposing mucus of the urinary bladder, or any other putrefying animal matter, such as albumen.

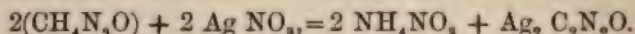
A solution of urea, when heated with caustic lime, or magnesia, to a temperature of above 50° C., will evolve ammonia. Below 50° C., lime and magnesia exert no influence upon urea in solution, and may therefore be employed with safety for the quantitative analysis of ammonia in urine.

A solution of urea, when mixed with liquor sodæ chlorinatæ, evolves the whole of the urea in the form of nitrogen, carbonic acid, and water. As the carbonic acid is immediately absorbed, nitrogen only is left, the bulk of which, on measuring, is a ready

means of determining the amount of urea of which it was a part (Method of E. W. Davy; "Dublin Hosp. Gaz." June 1, 1854; "Philos. Mag." June 1854, p. 385).

A solution of urea, when mixed with an excess of hypobromite of sodium, is rapidly decomposed so as to evolve about 90 per cent. of its nitrogen in a relatively short time. But the decomposition is never complete, and the reaction is therefore, notwithstanding the meritorious efforts of several chemists to make it applicable to what they call "clinical purposes," not adapted for accurate, or even approximately accurate estimations (see Schleich, "Journ. f. Pract. Chemie." 10 (1874), 261).

A mixture of urea and nitrate of silver in solution is on evaporation transformed into nitrate of ammonia and crystalline cyanate of silver. This experiment is the reverse of the process by which urea is produced artificially. Its formula is thus:



Combinations of Urea.

Urea enters into combination with several bases, acids, and salts. Of these compounds, those are of great importance which, by being insoluble in water and watery solutions, enable us to transform dissolved urea into a precipitate, and thereby to isolate it or determine its quantity.

Urea with oxyde of mercury.—*a. With one molecule of oxyde of mercury.* $\text{CH}_4\text{N}_2\text{O} + \text{HgO}$.—On adding to a warm solution of urea, oxyde of mercury diffused in water, we observe the first portions of the oxyde to be perfectly dissolved; an excess of the oxyde of mercury is in the fluid gradually changed into a white or yellowish white powder; the filtrate from the latter, after the elapse of twenty-four hours, deposits thin hard crusts on the walls of the vessel. These crusts and the powder have the above composition. The preparation frequently contains some cyanate of mercury.

b. With three molecules of oxyde of mercury. $2\text{CH}_4\text{N}_2\text{O} + 3\text{HgO}$.—On adding to a solution of urea, caustic potash, and then a solution of bichloride of mercury, with a renewed addition of potash ley, so that the fluid is always kept alkaline, a thick, gelatinous, snowy-white precipitate is obtained, which, when perfectly washed out and in its moist condition transferred into boiling water, transforms into a sandy or granular powder of a yellow or yellowish-white colour. After drying the powder is reddish-yellow. When heated while moist it frequently explodes, with evolution of light, water, carbonate of ammonia, and metallic mercury. The powder is soluble without effervescence in hydrocyanic and hydrochloric acid; in the latter solution alkalis produce a whitish-yellow precipitate.

c. *With two molecules of oxide of mercury.* $\text{CH}_4\text{N}_2\text{O} + 2\text{HgO}$.—If, instead of a solution of bichloride of mercury, a solution of nitrate of oxide of mercury is precipitated by an alkaline solution of urea, a white and less voluminous precipitate is obtained, which in boiling water shrinks to a sandy powder.

Urea and chloride of sodium. $\text{CH}_4\text{N}_2\text{O} + \text{NaCl} + \text{H}_2\text{O}$.—This salt crystallises in clino-rhombic prisms of great lustre, when a mixture of solutions of urea and chloride of sodium is evaporated. The same salt is obtained in large coloured crystals on evaporation of human urine.

Urea and nitric acid. $\text{CH}_4\text{N}_2\text{O} + \text{HNO}_3$.—If we mix a concentrated solution of urea, or urine concentrated by evaporation, with an excess of colourless nitric acid, the mixture will immediately crystallise into an almost solid mass of white shining scales or plates (yellow from urine) of nitrate of urea. This crystallisation may be completed or accelerated by exposing the mixture to the influence of cold.

Nitrate of urea crystallises in the rhombic system. If a pure crystallisation be obtained, the rhombic prisms may be seen to perfection. They are either flat, single, and primary, or combinations of several prisms, like those of pure urea, becoming hexagonal, and ultimately thin plates.

The nitrate obtained from urine directly, almost always crystallises in large plates, of which many lie upon each other, mostly with their principal crystallographical axes parallel to each other. This parallelism is observed also in crystallisations of pure urea; the plates only show the prismatic character a little more.

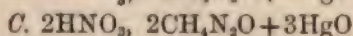
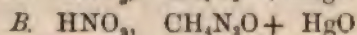
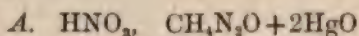
Nitrate of urea is not changed by the influence of the air. It is soluble in water. Heated on platinum foil it explodes, when the temperature has been raised quickly to a high point; but if only heated to 140°C . it decomposes, carbonic acid, suboxide of nitrogen, urea, and nitrate of ammonia being produced.

Urea and oxalic acid. $(2\text{CH}_4\text{N}_2\text{O}, \text{C}_2\text{H}_2\text{O}_4)$.—Oxalic acid has a stronger affinity for urea than nitric acid, so that when it is added to a solution of the nitrate, oxalate of urea will be formed, which not being very soluble in water containing nitric acid, is precipitated. Oxalate of urea crystallises in rhombic prisms and rhombic plates, some varieties of which are very much like the prismatic plates of nitrate of urea. But frequently the oxalate has more tendency to produce crystals in which the axes are of a more equal length; these crystals, though smaller in outline have then more body. To the naked eye a precipitate of the oxalate of urea appears as a white crystalline mass of plates. This salt is soluble in 23 parts of water of a temperature of 15°C ., but is soluble in a much smaller quantity of boiling water.

Urea and nitrate of mercury (Liebig, "Ann. Chem." 85, 294.)

—On adding to a solution of urea a solution of nitrate of mercury, a white flocculent precipitate is immediately produced, which contains urea, oxyde of mercury, and nitric acid. According to the proportion in which both solutions are mixed, and the amount of free acid contained in the solution of mercury, one of three compounds, or a mixture of three compounds, is produced, which are distinguished from each other by containing different quantities of the oxyde of mercury.

These three different combinations have the following characters in common:—On combustion with oxyde of copper they develop a mixture of gases, in which nitrogen and carbonic acid are present in the proportion of three volumes of the one to two volumes of the other. This is the same proportion as in the nitrate of urea. On removing the oxyde of mercury by sulphuretted hydrogen, there remains in the fluid after filtration from the precipitate, pure nitrate of urea, which crystallises to the last drop. These combinations, therefore, only differ from each other by a varying amount of oxyde of mercury; they are entirely soluble in hydrocyanic acid and hot nitric acid. In the latter solution, potash produces a white precipitate. If the dry precipitate of one of them is heated for a length of time in a current of warm air, a decomposition takes place; it assumes a yellowish colour, and the solution in nitric acid gives now a yellowish precipitate with potash. The formulæ of these three combinations are—



From these formulæ, and the manner in which they are decomposed by sulphuretted hydrogen, sulphuret of mercury being precipitated and nitrate of urea going into solution, we may consider these bodies to be combinations of one molecule of nitrate of urea, with two, one, and of two molecules of urea nitrate with three molecules of the oxyde of mercury respectively. The first of these combinations is produced in the quantitative analysis of urea in the urine.

*Method of ascertaining the quantity of Urea in
Urine volumetrically.*

This mode of ascertaining the quantity of urea dissolved in urine is based upon the property of urea to be precipitated by the addition of nitrate of mercury, in combination with one molecule of nitric acid and two molecules of the oxyde of mercury, three molecules of nitric acid remaining free in solution.

On gradually adding to a dilute solution of urea a dilute

solution of nitrate of mercury, and neutralising the free acid of the mixture from time to time by the addition of some baryta water or a dilute solution of carbonate of soda, a flocculent, bulky, snowy-white precipitate is obtained, which is insoluble in water. If the alternate addition of the nitrate of mercury and carbonate of soda be continued as long as a precipitate is formed, there will be a point at which the mixture, or the spot where the drop of the solution of the carbonate falls into the mixture, will assume a yellow colour, owing to the formation either of oxyde of mercury, or basic nitrate of mercury, or carbonate of mercury. If the fluid is now filtered, it does not any longer contain any appreciable quantity of urea; the whole of the urea has been precipitated. The precipitate is composed of one molecule of urea, and two molecules of oxyde of mercury. By mixing solutions of urea and nitrate of mercury, both of known strength, we can easily convince ourselves that precipitation of the yellow oxyde or carbonate by the addition of carbonate of soda does not take place until we have added, for ten parts of urea in the solution of urea, a volume of the solution of mercury, in which there are contained seventy-seven parts of the oxyde of mercury. This amounts to two molecules of the oxyde for one molecule of urea.

If we continue adding a solution of nitrate of mercury to a solution of urea so long as a precipitate is produced, the mixture will remain *white* on the addition of carbonate of soda. But if the original mixture be allowed to stand for several hours, the precipitate after the lapse of that time will have changed its properties, and have become crystalline. One may now easily recognise the six-sided plates of the combination of two molecules urea nitrate with three molecules of the oxyde of mercury; and the clear fluid which stands over the precipitate, and which, on the admixture of an alkali, gave a white precipitate, is now precipitated *yellow* by the same alkalies. In the acid fluid the combination, containing two molecules of the oxyde of mercury and one of nitric acid, is reduced to a combination containing less oxyde, because a part of the oxyde is redissolved by the free acid of the fluid.

In order to recognise whether an amount of the solution of the nitrate of mercury sufficient to produce the combination of urea with two molecules of the oxyde of mercury has been added, the neutralisation with carbonate of soda after the addition to the solution of urea of the mercurial solution becomes necessary. If a drop of the mixture, when added to a drop of a solution of carbonate of soda on a watch-glass, or on a flat piece of glass, remains white, we may be quite sure that there still is uncombined urea in the mixture. When, however, on the two drops mixing, a yellow pellicle is produced, then we have added a sufficient amount, or rather a little more than sufficient, of the

mercurial solution to precipitate the whole of the urea. It requires only a small excess of the salt of mercury to indicate that the quantity sufficient to precipitate all the urea has been added. It is therefore evident, that if we know the amount of mercury contained in the solution of it, we may, from the quantity of this solution used for precipitating urea in the manner described, determine the quantity of urea contained in solution; or if, for precipitating a *known* quantity of urea, say 100 milligrammes, we have used a certain volume of the solution of mercury, this same volume of the same solution will indicate the same quantity of urea in fluids containing an unknown amount of urea. From the volume of the mercurial solution used in this way, the amount of urea present may then be calculated; a consumption of half the volume shows half the amount of urea, of twice the volume double the quantity of urea, to be contained in the fluid.

*Preparation of the Solution of Mercury for precipitating
Urea from Urine.*

Four grammes of pure urea are first dissolved in water, and this solution is diluted with water to exactly the bulk of 200 c.c. By dissolving four grammes of urea in 200 c.c. of water, 201.75 c.c. of solution would be obtained, being 1.75 c.c. in excess.

Of the solution of nitrate of mercury, which is to serve for the purpose of precipitating urea from the urine, 20 c.c. are to be just sufficient to indicate exactly the amount of urea contained in 10 c.c. of the solution just described, namely, 200 milligrammes of urea; one cubic centimetre, therefore, of the mercurial solution must correspond with 10 milligrammes of urea. To this end, the solution of mercury must contain an amount of oxyde sufficient to produce, with 10 milligrammes of urea, the nitrate containing two molecules of the oxyde of mercury, and further, it must contain a trifling excess of the oxyde of mercury, in order to indicate the complete precipitation of the urea. This is the case when, after the addition of the last drop of the 10 c.c. of the mercurial solution to the solution of urea, a solution of carbonate of soda produces a distinctly yellow-coloured precipitate.

According to calculation, 100 milligrammes of urea require for precipitation 720 milligrammes of the oxyde of mercury (in the form of nitrate); but in order to produce a distinct reaction of oxyde of mercury in dilute solutions of urea, the 10 c.c. of mercurial solution necessary to precipitate the 100 milligrammes of urea must contain an excess of oxyde amounting to 52 milligrammes, or in all 772 milligrammes of oxyde. Every cubic centimetre of the solution, therefore, must contain an excess of 5.2 milligrammes of oxyde.

The simplest mode of obtaining the test-fluid is by dissolving

in a glass beaker one part of pure metallic quicksilver in five parts of nitric acid of 1.425 specific gravity, and frequently adding a little nitric acid, keeping the mixture at a gentle heat, until the evolution of vapours of nitrous acid has entirely ceased. The solution is then evaporated on the water-bath until it assumes the consistence of a syrup. This syrup is then diluted with water until 100 c.c. of this dilute fluid contain exactly 7.140 grammes of mercury. This is the case, if 100 grammes of mercury, after transformation into the nitrate of the oxyde, are dissolved in so much water that the bulk of the solution amounts to exactly 1400 c.c.

If we use for the preparation of the oxyde the crystallised nitrate of the suboxyde of mercury, which may with greater facility be obtained pure, and is more free from other metals than metallic mercury, the concentrated solution of the oxyde obtained is of unknown strength. The quantity of oxyde contained in it must therefore be determined; and this being done, the solution is to be diluted to the strength already stated.

There are several methods of finding the amount of oxyde of mercury contained in a solution of the nitrate. It may be found in a direct way by diluting a known volume of the concentrated solution or syrup with ten volumes of water, and precipitating the oxyde of 10 c.c. of this solution by the addition of potassa. Or a precipitate of the sulphide of mercury may be obtained by mixing the nitrate with a solution of sulphate of soda, and decomposing the precipitated sulphate of oxyde of mercury by a current of sulphuretted hydrogen.

A third proceeding, which dispenses with scales, is the following:—

Episode: Mode of ascertaining the amount of oxyde of mercury contained in a solution of nitrate of mercury.—On mixing a solution of the nitrate of oxyde of mercury with a solution of phosphate of soda, a white flocculent precipitate of phosphate of oxyde of mercury is immediately produced, which, on being allowed to stand in the liquid, rapidly becomes crystalline.

A solution of corrosive sublimate may, however, be mixed with the alkaline phosphate, without any turbidity being produced.

If to the mixture of the two first-mentioned salts we add a solution of chloride of sodium, before the precipitate has had time to become crystalline, the latter immediately decomposes with the chloride of sodium, corrosive sublimate and phosphate of sodium being produced; the precipitate disappears, and the fluid becomes perfectly clear.

This test is the basis of the following method, by which the amount of protoxyde of mercury contained in a solution of the nitrate may be ascertained with tolerable accuracy. One molecule of phosphate of mercury requires for its redissolution two molecules

of chloride of sodium. It follows from this that if we know the amount of chloride of sodium which it has been necessary to add for redissolving the phosphate of mercury, we also know the amount of oxyde contained in the solution of the nitrate.

As the atomic weight of the chloride of sodium is only about one-quarter of that of the oxyde of mercury, a slight error in the addition of the chloride of sodium will be quadrupled in the calculation of the mercury. This analysis is therefore not so accurate as its reverse, the determination of chloride of sodium by the mercurial solution. But it is sufficiently accurate for the purpose here intended.

Episode in episode: Preparation of the standard solution of chloride of sodium to be employed in ascertaining the amount of mercury in solution.—A saturated solution of chloride of sodium is first prepared by pouring water over pure, transparent rock salt in coarse pieces, and letting it stand for solution at a temperature of from 12.2 to 23.9°C. If the mixture be frequently shaken it will, after the lapse of twenty-four hours, be perfectly saturated, and in every case will contain an invariable amount of salt, viz., 3.184 grammes in every 10 c.c. The solution, after decanting and filtering, is ready for use.

Of this solution we take with a pipette	20.0 c.c.
And add water	566.8 c.c.
Whereby we obtain of dilute solution	<hr/>
of chloride of sodium	586.8 c.c.

which in all contain 6368 milligrammes of chloride of sodium, viz., the amount contained in 20 c.c. of the saturated solution. In 10 c.c. of this dilute solution there are consequently contained 108.52 milligrammes of chloride of sodium, corresponding to 200 milligrammes of oxyde of mercury (1 c.c. dilute solution = 20 milligrammes of oxyde of mercury). This calculation is based upon the atomic weight of oxyde of mercury = 216, and chloride of sodium = 58.6, which stand to each other in the same proportion as 400 of the oxyde to 108.52 of chloride of sodium.

Mode of ascertaining amount of Oxyde, &c. (continued).—In order to determine with some degree of accuracy the amount of oxyde contained in a solution of the nitrate, the latter must not be too concentrated, partly because a larger bulk admits of more accurate measurement, partly because the end of the reaction is much more perceptible in dilute than in concentrated fluids. It is therefore desirable that the mercurial solution, which is to serve for the test, should in 10 c.c. not contain more than from 180 to 200 milligrammes of oxyde of mercury.

The following preliminary experiment is therefore made, for the purpose of ascertaining the concentration: 10.0 c.c. of the solution of chloride of sodium are mixed with 4.0 c.c. of a solu-

tion of phosphate of sodium (the officinal salt) saturated at the ordinary temperature. To this mixture the mercurial solution is now poured from a burette, until a precipitate is formed which does not disappear on shaking the fluid. Let us suppose that we have used for that purpose 2.4 c.c. of the mercurial solution; they accordingly contain 200 milligrammes of oxyde; 10 c.c. of the solution therefore contain more than 800 milligrammes, when they should only contain 200 milligrammes at the outside. This solution, therefore, before the actual testing begins, must be diluted with three times its own volume of water.

Of this dilute solution of mercury we now measure 10.0 c.c. into a beaker, add 4.0 c.c. of the above-mentioned solution of phosphate of sodium, and pour from a burette the graduated or standard solution of chloride of sodium into this mixture, which is kept in constant agitation, until at last the white precipitate, which is formed on addition of the phosphate to the mercurial solution, is entirely redissolved.

The addition to the mercurial fluid of the solution of phosphate of sodium must be followed immediately by that of the chloride of sodium; for if we suspend the addition of the latter only for a few minutes, the phosphate of mercury becomes crystalline, and now either dissolves not at all, or with difficulty only. The solution of mercury, moreover, must not contain too much free acid. It contains the proper amount, if, after the addition of the phosphate of sodium, the mixture no longer reddens litmus. If it has, however, an acid reaction, the mercurial solution must, previously to the testing, have a part of its acidity neutralised by the addition of a few drops of a solution of carbonate of sodium, until basic salt begins to be precipitated, which may be redissolved by a drop or two of dilute of nitric acid.

As a matter of course the errors in this analysis are mainly due to our adding a drop or two more of the chloride of sodium than is actually required to dissolve the precipitates. The greater the quantity of solution of chloride of sodium added to a given bulk of the mercurial solution, the more oxyde this solution will appear to contain. The error, consequently, which we have just pointed out, increases the apparent real amount of oxyde contained in the solution. As the phosphate of mercury is slightly soluble in the fluid, and as, after all, the solution of chloride of sodium is graduated with regard to this error, the latter is generally very slight. If the proceeding be reversed by pouring the mercurial solution into a mixture of the solution of chloride of sodium and the alkaline phosphate, a slight excess of the mercurial solution must always be added, for the purpose of producing the precipitate, which is not permanent until the fluid has been saturated with the mercury. This proceeding, therefore, would give too low an indication of the amount of oxyde.

These analyses become still more correct, if we combine both methods, and proceed in the following manner:—

(Method I.) We measure 10 c.c. of the solution of mercury into a beaker, add from 3 to 4 c.c. of the solution of phosphate of sodium, and, taking care not to let the precipitate become crystalline, we immediately pour from the burette into the fluid the solution of chloride of sodium, until the precipitate has disappeared. Let us suppose that we have used for that purpose 12.5 c.c. of the solution of chloride of sodium, we now—

(Method II.) Measure 12.5 c.c. of the same solution of chloride of sodium into a beaker, add from 3 to 4 c.c. of the phosphate of sodium, and pour into this mixture from a burette the amount of the same solution of mercury, which is just necessary for the production of a commencing precipitate. Let us suppose that we have used of it 10.25 c.c., then its real strength is—There have been used for

I. 10.0 c.c. of the merc. sol.	12.5 c.c. sol. of chl. of sod.
II. 10.25 c.c. ditto.	12.5 c.c. ditto.
20.25 c.c. merc. sol.	25.0 c.c. sol. of chl. of sod.

As every c.c. of the graduated solution of chloride of sodium indicates 20 milligrammes of oxyde of mercury, it follows that the 25 c.c. used indicate $20 \times 25 = 500$ milligrammes of oxyde, which are contained in 20.25 c.c. of mercurial solution.

In this manner has been ascertained the amount of oxyde contained in the solution (diluted with three volumes of water). I will now proceed to give the description of the other proceedings necessary for producing a solution graduated for urea.

Preparation of Mercurial Solution graduated for Urea
(continued).

A known volume of the concentrated solution or syrup, in a part of which, after dilution with three volumes of water, the amount of oxyde of mercury has been ascertained, is now diluted with so much water as will bring it near to the point of concentration required for urea. The correctness of this dilution must be checked before its application for determining the amount of urea in urine, by means of the solution of pure urea mentioned above, which in 10 c.c. contains 200 milligrammes of urea.

In diluting the concentrated mercurial solution, it is advisable not to add the whole bulk of water, which by calculation has been found necessary, all at once. It is better to add a little less water, then to test with the solution of urea, and after thus checking the correctness of the analysis, to add the rest of the water.

To recapitulate the entire proceeding:

We take 10 c.c. of the concentrated solution or syrup, dilute it with five or ten times its bulk of water, according to its concentration, and in 10.0 c.c. of this dilute solution we approximately ascertain the amount of oxyde by means of the phosphate of sodium and the graduated solution of chloride of sodium.

Let us suppose that for 10.0 c.c. of the solution diluted with five times its own bulk of water we have used 18.5 c.c. of the solution of chloride of sodium, the amount of water to be added can then easily be calculated.

For 10.0 c.c. of the concentrated solution there ought to be used 38.5 c.c. of the graduated solution of chloride of sodium (corresponding to 772 milligrammes of oxyde of mercury). We have, however, in reality used $5 \times 18.5 = 92.5$ c.c. of the graduated solution. If for 10.0 c.c. of the concentrated mercurial solution there are required 92.5 c.c. of the graduated solution of chloride of sodium, 4.16 c.c. of the former will exactly be necessary to neutralise 38.5 c.c. of the latter. If therefore

416 vol. of the concentrated merc. solut. are mixed with
584 vol. of water, we obtain

1000 vol. of a dilute solution,

10.0 c.c. of which exactly correspond to 38.5 c.c. of the graduated solution of chloride of sodium.

As has been already stated, it is not advisable to add the whole amount of water (the whole 584 volumes) at once. It is better to allow a margin. We now measure 10 c.c. of the graduated solution of urea into a beaker, add from a burette the solution, which has been diluted to not quite the calculated strength, until a drop of the mixture, when brought into contact with a drop of a solution of carbonate of sodium on a glass plate or a watch-glass, gives a distinct yellow reaction. In case we have used for that purpose 19.25 c.c. of the solution of mercury,

We now add upon every	.	.	192.5 c.c. of the latter,
Water to the amount of	.	.	7.5 c.c.

Whereby we obtain a total of solution = 200.0 c.c.

We now make the final experiment with this solution.

If after the addition, to 10 c.c. of the solution of urea, of 20 c.c. of the mercurial solution, the yellow colour appears distinctly, the solution of mercury may be used for ascertaining the amount of urea in urine.

We must bestow all possible care upon the correctness of the test-fluid, as it is intended to replace the balance, which, when faulty, will make the error appear the larger, the smaller the

difference of weight we wish to determine. In the case of an incorrect balance, the error may be met every time we use it—it is possible to weigh correctly with it. But a graduated fluid must be corrected once for all before use. The volume of the fluid does not increase the trouble of preparing it; and it is therefore advisable to prepare the largest possible quantity at one time.

The small excess of the oxyde of mercury in the fluid is like the hand of the balance; the yellow colour is its deflection, the amount of which must be carefully impressed upon the memory.

Analysis of Urea in Urine. Special Proceedings.

We first prepare a mixture of two volumes of baryta water, and one volume of a solution of nitrate of baryum, both saturated at the ordinary temperature. Of this alkaline fluid, one volume is mixed with two volumes of urine. For this purpose a pipette of a capacity of 15 c.c., may be used. It is twice filled with urine, afterwards *once* filled with solution of baryta, and the latter is poured on the urine in a beaker. The precipitate which forms when the two fluids mix is removed by filtering. Of the filtered fluid, 15 c.c., corresponding to 10 c.c. of urine, are taken for each analysis.

To this volume of urine we now, without neutralising, add from a burette the graduated solution of the nitrate of oxyde of mercury, keeping the mixture agitated all the time, and test the mixture as soon as we perceive that no further precipitate is formed, and that the fluid does no longer become thick on the addition of the mercurial solution. For this purpose we take with a glass rod a drop out of the mixture, and add it to a drop of a solution of carbonate of sodium, of which there are several in readiness on a glass plate lying on a sheet of white or black paper. If after the lapse of a few seconds the mixture of the two drops remain white, the addition of the mercurial solution must be repeated, until, on a new trial, a drop of the contents of the beaker exhibits a distinct yellow colour on being added to the drop of solution of carbonate of sodium.

We now read on the scale of the burette the number of cubic centimetres of the mercurial solution used; and from this ascertain, by the simplest calculation, the amount of urea contained in 10 c.c. of urine, and hence in the total quantity discharged in twenty-four hours.

Modification of this method required by an excess of urea in urine.—The mercurial test-fluid is graduated for a solution of urea containing 2 per cent. of this substance: 15 c.c. of the solution of urea required for precipitating the whole of the urea, and for the production of the test indicative of the completion of the

precipitation, 30 c.c. of mercurial solution. We thus obtain 45 c.c. of a mixture in which on the whole there are 30 times $5.2 = 156$ milligrammes of free oxyde of mercury; every cubic centimetre therefore contains 3.47 milligrammes of oxyde of mercury.

If the 15 c.c. of solution of urea contain 4 per cent. of urea, and we add 60 c.c. of the mercurial solution, a mixture amounting to 75 c.c. is produced, in which there are contained 312 milligrammes of the oxyde of mercury, viz., 4.16 milligrammes in every cubic centimetre, being an excess of 0.69 milligrammes of oxyde in every cubic centimetre above what is required to produce the original colour.

It has been shown by careful experiment that, in analysing urine containing a larger amount of urea, an error is committed which makes the amount of urea appear smaller than it really is. In the case just now given as an illustration, we would not add 60 c.c. of the mercurial solution for the production of the original colour, but only 59.37 c.c. In order to remove this error, we have only to make the mixture more dilute by the addition of water. As soon as we have found out that the urine contains a higher percentage of urea than the mercurial solution is graduated for—for example, if more than 30.0 c.c. of the mercurial solution are used for 15 c.c. of urine—we must, for the number of cubic centimetres of the mercurial solution above 30.0 c.c., add half the number of cubic centimetres of water *before testing with carbonate of sodium*. If, for instance, we have used 20 c.c. more than 30, we add 10 c.c. of water. It will always be found that, after the addition of the water, a few more drops of the mercurial solution must be added before the proper indication is obtained.

Modification required by the urea sinking to 1 per cent.—If the quantity of urea in urine amounts to 1 per cent. only, it will be necessary to add to 15 c.c. of urine not 15 c.c. only, but 15.3 c.c., which would unduly increase the apparent amount of urea. To avoid this error in working with dilute urine, we must, for every 5 c.c. of mercurial solution which have been used less than 30 c.c., subtract 0.1 c.c. from the sum of cubic centimetres actually used. If therefore for 15 c.c. of urine 25.0 c.c. of mercurial solution have been used, the *real* amount of urea being 249 milligrammes, is expressed by 24.9 c.c. of mercurial solution.

Modification required by the presence in urine of chloride of sodium.—A series of experiments has shown that, when the chloride of sodium contained in urine amounts to 1 or 1.5 per cent., it interferes with the analysis of urea by means of the mercurial solution. If to 10 c.c. of the solution of pure urea 20 c.c. of the graduated mercurial solution are added, carbonate of sodium will produce a distinct yellow precipitate of oxyde of

mercury in the mixture. If to the latter we now add from 100 to 200 milligrammes of chloride of sodium, and test again with carbonate of soda, the yellow colour will not appear, and for its reproduction will require a further addition of from 1.5 to 2.5 c.c. of the mercurial solution; which, if taken as representing urea, would increase the apparent amount of the latter by 15 to 25 milligrammes.

It is the same in urine. The chloride of sodium contained in it increases the apparent amount of urea unduly by 20 or 30 milligrammes in 10 c.c. In case the amount of chloride of sodium rises above 2 per cent., the error is not increased in proportion to the quantity, but remains the same, with certain fluctuations.

As we shall see more particularly in treating of the determination of chloride of sodium by means of the nitrate of oxyde of mercury, a solution of urea containing chloride of sodium is not precipitated until all the chloride of sodium present is decomposed, and corrosive sublimate is formed. In a solution of 200 milligrammes of urea and 100 milligrammes of chloride of sodium in 10 c.c. of water, to which 20 c.c. of the mercurial solution have been added, the excess of the mercury, which otherwise would have given the yellow reaction on addition of carbonate of sodium, is not present in the form of nitrate, but of corrosive sublimate; by the formation and presence of which, it is evident, the change in the test is caused. Instead of 3.46 milligrammes of oxyde of mercury in the form of nitrate, the mixture contains the same amount of mercury in the form of sublimate.

On diluting a solution of corrosive sublimate with water until it yields a distinct brownish-yellow precipitate of oxychloride of mercury on the addition of carbonate of sodium, and on then mixing the same solution of sublimate with a drop of nitric acid, and then adding it in drops to a solution of carbonate of sodium, the mixture will remain clear. No precipitate will be formed; and, if any, it consists only of a slight whitish turbidity, from which, after prolonged standing, some few brownish-yellow plates are deposited. In this condition the excess of corrosive sublimate exists in the mixture of the solutions of urea and of mercury, the greater part of the nitric acid of which is in a free and uncombined state.

This free nitric acid converts part of the carbonate of sodium into the bicarbonate, which does not precipitate corrosive sublimate. When the mixture, in consequence of a larger amount of chloride of sodium having been present in it, contains a larger amount of corrosive sublimate, the quantity of carbonic acid set free is not sufficient to totally prevent the precipitation of oxyde of mercury, and a brownish-yellow precipitate is produced. This appears to be the reason why

the presence of a certain amount of chloride of sodium defers the indication of the complete precipitation of urea, and why a further increase in the amount of chloride of sodium does not interfere with the test after having reached a certain height.

In operating upon urine containing from 1 to 1.5 per cent. of chloride of sodium, the number of milligrammes of urea contained in 10.0 c.c. of urine may at once be correctly obtained by simply subtracting 2 c.c. from the total cubic centimetres of mercurial solution used. The results thus obtained are relatively correct as regards the differences of the amounts of urea, even when the quantity of chloride of sodium varies in the urine of different individuals. There is only a slight error in the absolute quantity of urea, which, if left uncorrected, may amount to 15 or 20 milligrammes in 10 c.c. of urine.

If, therefore, we require to know the absolute quantity of urea in urine, the chlorine must be removed from the urine, and the chloride of sodium converted into the nitrate. This is done by the agency of a graduated solution of nitrate of silver. 11.601 grammes of fused nitrate of silver are dissolved in water and diluted until the volume of the fluid amounts to 400 c.c. One cubic centimetre of this solution contains 29.01 milligrammes of nitrate of silver, corresponding to 10 milligrammes of chloride of sodium.

The solution of mercury, which will be described under the head of chloride of sodium, corresponds to this solution of silver. Equal volumes of both will, on use, indicate equal quantities of common salt. If, therefore, to 10 c.c. of urine we had to add 12.5 c.c. of the mercurial solution just alluded to, for producing the turbidity indicating that all the chloride of sodium is converted, then 12.5 c.c. of the solution of silver, on being added to 10 c.c. of urine, will precipitate the whole of the chlorine without any silver being left in solution.

As, by means of the mercurial solution, we can ascertain in a few seconds how much of the solution of silver it is necessary to add to urine containing chloride of sodium, for the purpose of removing the latter, this operation, which otherwise would be laborious and take much time, is divested of all inconvenience.

Let us suppose that for 15 c.c. of urine precipitated with the solution of baryta, corresponding to 10 c.c. of the original urine, we have used 17.5 of the mercurial solution graduated for common salt. We now measure with a pipette

30.0 c.c. of the same urine, add
35.0 c.c. of the solution of silver,
<hr/>
65.0 c.c.

and throw the mixture on a filter.

Of the filtered liquid we now take for the test of urea always one-half of the number of cubic centimetres of the mixed fluid, viz., 32.5 c.c., in which there are contained 10 c.c. of urine, less phosphates and chlorides. These are now mixed with the mercurial solution graduated for urea; and the quantity of the latter is thus ascertained, regard being always had to the dilution in consequence of the addition of the solution of silver.

Modification required by the urine containing ammonia.—For common urine, one volume of solution of baryta to two volumes of urine is generally sufficient for precipitating the whole of the phosphoric and sulphuric acid present, and leaving a small amount of baryta in solution. If, however, the urine becomes alkaline from the presence of an alkaline carbonate, which most commonly is carbonate of ammonium, from the decomposition of urea, one volume of solution of baryta to two volumes of urine is in most cases insufficient to precipitate the whole amount of carbonic acid. It therefore will be necessary to add a larger amount of the solution of baryta.

If three volumes of the solution of baryta are mixed with four volumes of urine, 17.5 c.c. of the filtered fluid, corresponding to 10 c.c. of urine, will have to be taken for the analysis of urea by precipitation. Of a mixture of equal volumes of solution of baryta and urine, 20 c.c. must be taken for the test; and so on in the same proportion.

The influence of the decomposition of urea will in many cases not prevent the same results from being obtained in putrid urine as were arrived at in the same urine when fresh. Two or three days' standing will generally make no difference; but after that, the analysis with the mercurial fluid cannot any longer be depended upon.

If exact analyses of ammoniacal urine be required, we may either fix the carbonic acid, and transform the urea present into the same acid and ammonia by subjecting a quantity of urine to Bunsen's analysis; or we must determine the ammonia and urea each by a separate process in two separate portions of urine, and calculate the amount of urea from the ammonia by which it is represented.

For the analysis of urea in this kind of urine, it is not precipitated with the mixture of solutions of baryta, but with baryta water only. From the filtered fluid a portion is taken corresponding to 10 c.c. of urine, and heated in a water-bath, until ammonia is no longer evolved. This expulsion of ammonia is easily effected, because, after the addition of baryta water, which, when added in sufficient quantity, combines with the whole amount of carbonic acid present, the whole amount of ammonia is contained in the form of caustic ammonia. In the fluid thus freed of ammonia, urea is determined by the mercurial fluid.

W. A. SELL

In another portion of the urine the ammonia has to be determined by one of the ordinary alkalimetric methods. The most convenient test is dilute sulphuric acid, which may be procured by mixing 16.333 grammes of pure hydrated sulphuric acid with as much water as will raise the whole of the mixture to 500 c.c., or 1000 half c.c. Of this sulphuric acid 0.5 c.c. exactly saturate 5.66 milligrammes of ammonia, being the quantity produced by the decomposition of 10 milligrammes of urea. Every cubic centimetre of sulphuric acid, therefore, used for neutralising the ammonia of urine, corresponds to 20 milligrammes of urea originally contained in the urine.

The analysis becomes more accurate if we subject a known quantity of urine (after treatment with baryta) to distillation, collect the product in a receiver containing a known volume of the graduated sulphuric acid, which must be more than sufficient for neutralising the whole amount of ammonia that passes over. The quantity of free acid left is then determined by means of a dilute solution of ammonia, graduated upon the dilute and graduated sulphuric acid. If, for example, we have put into the receiver 40 c.c. of dilute sulphuric acid, and if, after partial saturation by the distillate, we yet require 15.0 c.c. of the graduated solution of ammonia for neutralising the acid, then a quantity of ammonia has passed over by distillation which has neutralised $40 - 15 = 25$ c.c. of the graduated sulphuric acid, and represents 250 milligrammes of urea.

Modification required by the presence in urine of certain matters not being urea.—Besides urea, some other bodies are precipitated by the solution of nitrate of protoxyde of mercury. One of them is *allantoine*, as has been shown by Limpricht ("Ann. Chem." 1853, October, p. 99). It has been stated by Städeler that he found allantoine in the urine of dogs labouring under difficulties of respiration. Allantoine is present in the urine of the sucking calf; but it has never as yet been found either in the normal or pathological urine of man. Even under circumstances where its occurrence was most probable, as after the ingestion into the stomach of uric acid or urate of ammonia, when the usual products of the decomposition by oxydation of that body are found in the urine, viz., urea (an excess) and oxalic acid, the third produce of the artificial process, allantoine, could not be found in the urine by Wöhler. We may, therefore, be quite sure that our analyses will not easily be made inaccurate by the presence of that body.

There are, however, some matters, forming an insoluble precipitate with the nitrate of mercury, which are of more frequent occurrence, particularly in the urine of patients. Kletziński (Heller's "Archiv." 1853, p. 252), in his comparative experiments on the value of different methods for determining the quantity

of urea, found that there is a substance present in urine, which, by its property of being precipitated by a solution of sugar of lead, manifests itself as different from urea, and yet is precipitated along with urea by the mercurial solution. This substance, in five experiments made upon healthy urine, amounted to 2, 2, 3, 3, and 4 per cent. of the urea; but in the urine of patients it would rise to 12 per cent. of the urea present. Vogel is of opinion that the error in some cases might amount to 20 per cent. of the urea present.

This error Kletzensky proposed to avoid by the following proceeding:—Of a solution of sugar of lead, acidulated with a few drops of acetic acid, a sufficient quantity is added to urine to precipitate the whole of these matters. Any excess of the solution of lead must be removed by a current of sulphuretted hydrogen. After filtering and boiling, the urine may be used for the test for urea, due allowance being made for the dilution.

I have shown that these interfering substances are urochrome and kryptophanic acid. They cannot be entirely precipitated by neutral acetate of lead alone; basic acetate must be added to the urine, and afterwards an excess of this salt and some ammonia. Even then the entire amount of the acid is not yet removed, but is greatly diminished, and the analysis for urea may proceed.

*Analysis of the Urea-Nitrate Mercuric Oxide Precipitate
obtained in Liebig's Analysis for Urea.*

Two litres of the mercuric nitrate solution were made according to the prescription. A little baryta nitrate was added, which produced a slight deposit. The solution was allowed to stand for some weeks until brilliant, and then decanted. This precaution was taken because it had been ascertained that the mercuric solution always contained some sulphate. Some fresh healthy urine was now collected, and it was found that 10 c.c. of it, after treatment with baryta-mixture 15 c.c., required 21 c.c. of the mercurial solution for complete saturation of the urea. The total quantity of urine was now treated with baryta mixture, and of the filtrate 1320 c.c. were mixed with 1848 c.c. of mercuric solution. The liquid, tested with sodium carbonate, produced the standard reaction.

The precipitate was allowed to stand some days, and was then washed with water by means of a syphon arrangement, until the wash water had a barely perceptible acid reaction. The precipitate, when dry, was slightly yellowish, and weighed about 38 grammes.

Analyses.—*Test for Ash.*—1.3175 grammes were ignited, and decrepitated violently. After complete combustion no residue was left. *Test for H_2SO_4 and \bar{S} .*—1.7130 grammes were

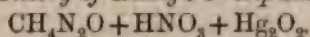
digested in aqua regia, and BaCl_2 added. No precipitate was obtained.

Determination of Mercury.—1.3705 grammes ignited in combustion tube with lime, &c., gave 1.0140 grammes Hg = 73.9 per cent.

Determination of Nitrogen.—0.7880 grammes burned with copper oxyde, &c., gave 51 c.c. of gas at 21°C . and 29.6 inch. B. 20 m.m. KHO column, equal to 45.9 c.c. N . = 0.0574 grammes = 7.2 per cent. N .

The nitrogen was free from nitric oxyde.

Theory of Liebig's Precipitate.



Atoms.	At. Wts.	In 100.	Found.
1C	12	"	"
5H	5	"	"
3N	42	7.56	7.2
6O	96	"	"
2Hg	400	72.07	73.9

555

These results are sufficiently near the theory to justify the conclusion that the precipitate obtained was really almost purely composed of urea-nitrate-mercuric oxyde. It dissolved, however, with difficulty only in boiling nitric acid, leaving after long boiling a barely perceptible insoluble residue. The solution gave no precipitate on adding silver nitrate, and therefore contained no chlorine.

The filtrate from the urea precipitate gave no precipitate on the addition of baryum nitrate, showing that no sulphuric acid could have been formed by oxydation after the removal of the urea.

Physiological Quantity of Urea.

Numerous experiments have shown that a healthy man, who lives well, discharges on an average from 30 to 40 grammes of urea in twenty-four hours, which, calculated upon one hour, gives 1.25 to 1.66 grammes. This average must of course vary a little according to the size of the individual; and in the individual it must be dependent on accidental circumstances, which will sometimes change it, and in rare instances will produce extreme maxima and minima. But for practical purposes the above figures are valuable, even though subject to the variations mentioned. It would be a much better basis for comparative researches at the bedside, if the average amount of urea could be expressed in proportion to certain units of weight of the body, say pounds or kilogrammes, or units of measure of length of body, say centimetres. As urea is the principal product of the

metamorphosis in the body of nitrogenised food, its quantity must stand in a direct relation to the quantity of food taken ; or, if little or no food be taken, to the amount of nitrogenised component parts of the body disintegrated in the place of food. In this sense must be taken the expression that urea is the measure of disintegration, or that the amount of urea is the measure of the preponderant part of the change of matter in the system. The *intensity* of the change is expressed by the *amount* of urea in the urine. A large amount of nitrogenised food taken into the stomach will increase the amount of urea above the average ; a small amount of vegetable food will make it sink below the ordinary medium.

In calculating the discharge of urea with regard to time, we must take care not to lose sight of the fact that the production of a given quantity within a certain time may appear larger or smaller according to certain circumstances, which retard or facilitate the secretion of the kidneys. If the amount of fluid discharged as urine become very small, the amount of urea discharged in a given time will also be smaller, owing no doubt to a part of the urea formed being retained in the system, particularly in the blood and muscles. If, on the contrary, the kidneys have to discharge a larger amount of water, the total quantity of urea will be raised above the average ; because an amount of urea which, under ordinary circumstances, would be retained in the system for a time, is discharged with this increased bulk of water. This is the case for solids generally, and we may well say that a large quantity of water acts as a diuretic so long as there are soluble substances in the blood to be carried away with it.

Pathological Indications.

If the amount of urea remain above or below the average for any length of time, so that the possibility of an accidental variation is excluded, it is a symptom of disease.

I will first consider the excess of urea. It is common in the stage of increment up to and over the acme of all acute febrile diseases, such as typhus and pneumonia, &c.; and the total quantity of urea discharged in twenty-four hours may amount to 50, 60, or 80 grammes, being double the amount of that discharged during health. This increase becomes a more important feature of disease, when the ingestion of nitrogenised matter falls to a minimum at the same time ; in other words, because these patients have mostly no appetite, and if they have, are obliged to restrain it by the dietetic rules of their medical attendant. As soon, however, as the fever has abated, the amount of urea will sink ; and that the lower below the normal quantity, the less food the patients are able to take from the continuance

of loss of appetite, or from the inadequacy of the organs of digestion to perform their task. But as the patients recover appetite and strength the amount of urea rises to its usual height. The same process is observed during the exacerbations of chronic disease, which in fact constitute an acute episode in the long train of symptoms. Thus an exacerbation of phthisis may be accompanied by urine similar to that of an attack of pneumonia, containing an excess of urea.

But in diseases which are chronic and accompanied by impaired nutrition the amount of urea sinks below the average.

The lowest amount of urea which I have ever observed to be discharged by a patient during twenty-four hours was 5 grammes, in 750 cub. cent. of pale, faintly alkaline urine. This was from a lady suffering from a tumour, and an anæmiated condition of the body. At the autopsy the tumour was found to be filled with and caused by fæces, which had escaped from the intestine through an ulcerated spot in its walls.

So low an amount of urea as 5 or 6 grammes in twenty-four hours generally only occurs towards the fatal end of diseases, when not only the production of urea is very limited, but also the excretory activity of the kidneys begins to become languid.

The diminution of the quantity of urea may, however, be due to the failure of the excretory activity of the kidneys only, though at the same time an excess may be produced in the system. The excess is then retained in the blood, tissues, and juices of the body, and causes the cachexia commonly known as uræmia. When urea is retained water is also mostly retained in part, and, by its effusion into the cavities and cellular tissue, causes dropsical disease. Urea may then be detected in most secretions, excretions, exudations, and effusions. It is the same with dropsical effusions from other causes: they contain in solution an amount of urea derived from the blood, but in these cases the impairment of the excretory activity of the kidneys is a secondary symptom, and scarcely ever causes that amount of retention of urea which may lead to uræmia. And even then the kidneys may be stimulated by diuretics or by exercise, or a spontaneous rally of the system may revive their excretory activity, when, with a large amount of urine, a proportionally large quantity of urea, which has been accumulated in the system, may be discharged. The amount of urea will here indicate the amount of depuration effected, just as in retention of urea the smaller amount discharged will allow us to calculate, taking the whole case into consideration, the amount produced, and, by subtraction, the amount retained in the blood.

CHAPTER IV.

URIC ACID.— $C_5H_4N_4O_3 + 2H_2O$.

HISTORY AND LITERATURE.

URIC acid was discovered and described by Scheele ("Kongl. Vet. Acad. Handbl." 1776, p. 327; Scheele's "Chemical Essays," p. 199) as the principal constituent of urinary calculi and deposits. Morveau ("Encycl. Méth. de Chim." art. Acides) gave it the name of lithic acid, which, at first adopted by Fourcroy ("Elements d. Chim." 4, 50), was by him afterwards exchanged for that of uric acid. Fourcroy and Vanquelin ("Ann. Chim." 16 (1793), 63; 27 (1799), 225) confirmed and extended the observations of Scheele. Brugnatelli ("Ann. Chim." 28 (1800), 56), in repeating the decomposition of uric acid by nitric acid, as already observed by Scheele, found "rosacic acid," the alloxan of the present day, and oxalic acid as products of that reaction. The first elementary analysis of uric acid was made, and its actual composition ascertained by Prout ("On the Nature and Proximate Principles of Urine," "Med. Chir. Transact." 1817; "Ann. Chim." 91 (1818), 379). Twenty years later the researches of Liebig and Wöhler ("Ann. Chem." 26 (1838), 241) on a variety of products of decomposition of this remarkable acid afforded great insight into its chemical nature and physiological significance. Many valuable and interesting researches have since that time been made, the results of which, as far as they concern the purpose of this work, will be mentioned in the sequel in their appropriate places.

Occurrence.—Uric acid is a constant ingredient in urine, from which it can be obtained in the crystallised state by precipitation with an acid, or combined with bases by concentration. It is the principal constituent of many sediments which occur in urine after cooling, or already in the urinary passages, and these frequently form concrements termed gravel, or larger calculi. In gout it is found in the blood and other juices of the body, and forms the principal ingredient of the concretions and diffuse deposits, which are found in various tissues, particularly in the proximity of joints. It is found in the urinary excretion of many classes of animals, from the mollusca upwards. The urine of birds contains a large amount of urates, so that 100 parts of

guano may be made (by the method of Bensch, "Ann. Chem." 58 (1846), 266; or of Löwe, "Erdmann's Journ." 96 (1865), 408) to yield from 2 to 20 parts of uric acid. The excrements of serpents consist of almost pure urate of ammonia, and therefore are the most convenient material for procuring pure uric acid.

Mode of obtaining it pure from the excrements of serpents.—The powdered excrements are dissolved in a hot ley of caustic potash or soda, containing one part of solid alkali in 10 parts of water, and boiled until ammonia is no longer evolved. The solution is now filtered through paper, after which a current of carbonic anhydride is made to pass through it until the precipitate, which at first is jelly-like, and consists of alkaline urate, becomes granular, and sinks to the bottom of the vessel as acid urate. The mixture should be allowed to stand for twenty-four hours to effect complete precipitation. The precipitate is then placed on a filter, and washed with cold water until the filtrates become turbid. The salt so obtained is again dissolved in hot dilute alkaline ley, and this solution is poured into hot dilute hydrochloric acid, which must be more than sufficient to neutralise all the alkali. Perfectly white and pure uric acid is precipitated; and after decanting, filtering, and washing, is dried. It consists of small scales, being mostly incomplete rhombic plates.

Mode of extracting it from human urine.—Fresh urine is filtered through coarse filtering paper, and mixed with about 5 per cent. of pure hydrochloric acid. It is then allowed to stand in a warm place for twenty-four hours, after which yellow or brown crystals of uric acid will be found floating on the surface of the fluid and adhering to the sides and bottom of the vessel. They are sunk by agitation with a glass rod, to which a piece of caoutchouc tubing is attached. When they have settled the fluid can be decanted and the deposit washed by water, to be removed by decantation. A brownish very fine deposit of altered colouring matter, which is easily roused by agitation, and differs greatly in appearance from the uric acid, may be removed with the washings. The crystals of uric acid are ultimately collected on a filter and dried. Uric acid can be obtained from urine by mere evaporation in the following manner:—The urine is evaporated to one-sixth, and filtered while warm. It is then slowly evaporated on the sand-bath until a pellicle forms on its surface. This, by cooling, becomes thick, and consists of uric acid and little urate. Decomposition by caustic alkali, spirit, and acid, will yield the uric acid in a pure state.

Mode of ascertaining the quantity of uric acid in urine.—In experiments where only approximative results are required, the uric acid obtained from a given quantity of urine with hydrochloric acid, by the process just mentioned, may be weighed. It

has been estimated by Heintz ("Poggend. Ann." 70 (1847), 122) that the loss incurred by the imperfect insolubility in acidulated urine of uric acid amounts to 9 parts in 100,000 of the urine used for the analysis, and that this loss is not increased by the presence of sugar, albumen, or the soluble constituents of blood. In all cases this loss is compensated by a certain amount of red or brownish colouring matter, which is strongly adherent to the particles composing the crystals. If the urine contain biliary products, the uric acid crystals may contain so much colouring matter that it may be necessary to purify them of it. This is best effected by dissolving the acid in alkali, adding spirit of wine to the solution, and precipitating it again by hydrochloric acid. The spirit retains the greater part of the colouring matter. The results obtained by the process of precipitation are subject to great variations, which mainly depend on the varying proportions between the quantity of uric acid and the amount of urine in which it is dissolved. Sometimes not a crystal of uric acid is obtained from a specimen of urine by treatment with acid, while a specimen of the same urine, treated by the processes to be described below, will yield a normal amount of it. In all cases, therefore, where the specific gravity of the urine is less than 1012, it is advisable to evaporate it until it shows about the normal specific gravity. As every 10,000 parts of urine retain one part of uric acid in solution, the evaporation of every 10,000 parts will increase the ultimate result by the amount of one part.

Concentrated urine, such as that of fever patients, when it has had no time to cool and deposit urates, sometimes lets fall a copious precipitate immediately on addition of an acid. This consists of amorphous hydrated uric acid, and becomes crystalline after standing some time, immediately when it is heated with the fluid. When precipitates of urates have been formed in urine in which uric acid is to be determined, they must either be redissolved in the entire amount of urine from which they have fallen, or separated by filtration, and the uric acid contained in them determined by a separate experiment.

In all cases of kidney disease, or other disorders of the urinary organs in which formed elements, such as casts of the uriniferous tubes, pus, blood, or cancerous cells are mixed with the urine, any urates that have fallen must, under all circumstances, be redissolved in the entire amount of urine by heating it in a water-bath to blood heat. The urine is then filtered at that temperature, and immediately mixed with acid, if it is desired to isolate and determine the quantity of uric acid.

When no urates have separated, simple filtration is a sufficient preparation for the treatment with acid of any specimen of urine, whether it be normal, or contain sugar, albumen, or any of the

soluble constituents of blood, or fatty serum, as in so-called chylous urine.

Second method.—As in the former method more or less uric acid remains in solution, the following process may be adopted where greater accuracy is desired. The urine after filtration is evaporated to the consistence of a syrup, treated with some hydrochloric acid, and extracted with alcohol. The insoluble part is treated with a dilute solution of potash, and some spirit is added to the solution, which is then filtered. It is made boiling hot, and acidified with hydrochloric acid, when all the uric acid is precipitated.

The uric acid may be conveniently extracted from the residue which remains after the extraction of hippuric acid. This residue is diluted with a little water, filtered, and the precipitate washed. After solution in potash, filtration and reprecipitation, uric acid in coloured crystals is obtained. In this and the former proceeding the admixture of some xanthine is possible. It can be extracted by an excess of ammonia.

The uric acid obtained by either of the above processes is dried, removed from the filter, and put into a watch-glass, or porcelain dish, or low glass bottle which can be covered or stoppered. It is next dried in the water-bath until it does not lose weight any longer. The vessel is now covered, and the closed apparatus allowed to cool over sulphuric acid under a closed receiver, and is then weighed. The weight of the vessel when empty deducted from its weight when charged, leaves the weight of the uric acid. Salkowsky (Virchow's "Archiv." 52, 58) has proposed to isolate the uric acid which is not precipitated by HCl, by argentic nitrate in an ammoniacal solution. For this purpose the urine filtered from the precipitated uric acid is made alkaline with ammonia, and the phosphoric acid is removed by magnesia mixture. An ammoniacal solution of argentic nitrate is added to the filtrate, and the precipitated compound placed on a filter, washed, and decomposed with hydrothion in alkaline solution. The filtrate, with acid, yields the uric acid. From later communications of Salkowsky (Pflüger's "Archiv." 5, 210), it appears that this precipitate is a mixture of argentic urate with the urate of the earth employed, in the above case magnesia, and a little ammonic urate. In no case was the precipitate found to have any definite constitution, and could therefore not be used for the determination of the uric acid without obtaining the latter in the free state. Schwanert ("Ann. Chem." 163 (1872), 153; Ber. D. Ch. G. 5 (1872), 316) finds that the method proposed by Salkowsky offers no advantage over the compensation by calculation according to Heintz, because a quantity of uric acid is lost in the precipitate of phosphates of earths by ammonia, and another quantity is lost by oxydation from reduced silver. The result is therefore less

accurate than the compensation, by calculation, and in no case rewards the trouble and loss of time experienced in its execution.

Physical Properties.—When to a solution of a urate hydrochloric acid is added, uric acid is precipitated as a jelly-like mass. This hydrate is transformed into anhydrous scales by warming the mixture. Dry uric acid is a white light powder, consisting of small delicate scales with irregular outline, of which the rhombic shape is mostly the origin.

Crystallography.—The purest and most perfect crystals of uric acid which can be obtained are oblong square plates, which might pass for rectangular and quadratic, but with the aid of other less common forms are recognised to be rhombic plates, with extremely obtuse angles. A secondary prism may take off the angles of the primary plate. When the secondary prism begins to predominate, we have a hexagonal plate. In this form uric acid is frequently obtained when precipitated from its ammoniacal solution by acetic acid. In this form it also crystallises from its solution in concentrated hydrochloric acid. In many cases the one pair of opposite angles of a plate become more acute, the other more obtuse, and plates may be observed varying from the rectangular form to that of needles. When crystallising slowly from a solution the needles of uric acid sometimes attain a length up to a quarter of an inch, and arrange themselves in sheaves or dendritically. To the foregoing elementary forms all crystals of uric acid occurring either as spontaneous deposits in the urine, or as products of a chemical process out of the body may be referred.

Occasionally twin crystals, composed of two rhombic plates crossing at right angles, or at an angle of 45° , are observed. There is another multiplication in which spinous crystals are placed upon a square plate, or imitate the square plate. This modification is usually large, and frequently obtained from urine by the addition of nitric acid. The student should reproduce all common varieties of form in order to enable himself to classify all the irregularities usually occurring in spontaneous deposits.

The common rhombic plates of uric acid deposits—when formed rather quickly round other matters, such as granules of urates—exhibit holes and other irregularities in their substance such as usually attend hasty formation. The obtuse angles frequently become rounded off, less frequently the pointed angles. In both cases the rhombic plates become oval. This rounding off of the obtuse angles produces the so-called lozenges. The shape of the crystals in pathological deposits, as well as in art-preparations, depends upon the concentration and temperature of the urine or solution, the presence or absence of abnormal or decomposed normal colouring matter, and its amount, and the nature and quantity of the acid by which uric acid is precipitated.

Uric acid polarises light, the large pure plates do so only faintly, because they are mostly covered with a sort of dew. The more transparent the crystals become, the more pronounced will become their chromatic polarisation. Crystals obtained from urine by acetic acid, and from a solution in hydrochloric acid are particularly suited for the experiment.

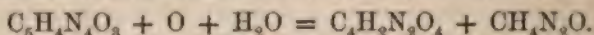
Chemical Properties.—The crystallised acid, on drying at 100° loses 25.5 per cent., or two molecules, of water of crystallisation. It is destitute of taste and smell. It is nearly insoluble in cold, sparingly soluble in hot water; one part of the acid requires for solution 1800 to 1900 parts of boiling water, and 14,000 to 15,000 parts of water at 20° . The watery solution faintly reddens litmus paper. The acid is a little more soluble in hydrochloric acid than in water. Boiling concentrated hydrochloric acid dissolves a quantity of uric acid, which is partly deposited in crystals on cooling, another part is obtained on evaporation of the acid. In concentrated sulphuric acid, uric acid is soluble without decomposition, and is precipitated from this solution by the addition of water. It is insoluble in alcohol and ether. It is with facility dissolved in a solution of the common phosphate of sodium, as also in solutions of many other salts of the alkalis, particularly at higher temperatures. In these cases uric acid combines with part of the base, and gives rise to the formation of acid salts, which impart to the solution an acid reaction.

Metamorphoses.—Uric acid is capable of undergoing, in the hands of the chemist, a very large number of metamorphoses into compounds of great general interest. Of these, however, only a limited number are of scientific importance in physiological and pathological chemistry, according to whether they show the antecedents of the acid, or its transformation into final products of the economy, or enable us to recognise it by means of what is ordinarily termed a chemical reaction.

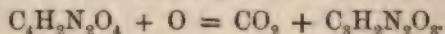
Amongst the metamorphoses of uric acid which might show its antecedents, are those into xanthine and hypoxanthine. This process of reduction or abstraction of oxygen is said to be effected by the agency of dilute sodium-amalgam upon a solution of uric acid in caustic alkali (Rheineck). The details and experimental proofs of this experiment have never been given, and it has moreover failed on repetition in the hands of several inquirers. The inverse operation, namely, the transformation of hypoxanthine into xanthine, and of the latter into uric acid, by the addition of oxygen, has also not yet been effected. Under the influence of heat uric acid is decomposed without being fused. By its dry distillation a sublimate is obtained, consisting of cyanuric acid, urea, ammonium carbonate, and ammonium cyanide. At the same time hydrocyanic acid escapes, and

some carbon remains behind, which is porous, and contains nitrogen.

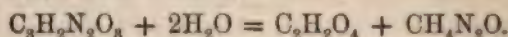
Concentrated nitric acid (4 parts of 1.42 spec. gr.) dissolves uric acid, (1 part) under effervescence, carbonic anhydride and nitrogen being disengaged. The reaction consists in the formation of alloxan, urea, and nitrous acid; the latter decomposing urea in the moment of formation into carbonic acid and nitrogen. Alloxan, $C_4H_2N_2O_4$, remains in large colourless rhombic octahedra, which are disintegrated under the influence of air, and are readily soluble in water. The solution reddens litmus paper, and imparts a purple colour to the skin. Under the influence of bromine uric acid is transformed into alloxan and urea—



Alloxan, on further oxydation, loses a molecule of carbonic anhydride, and is transformed into parabanic acid—

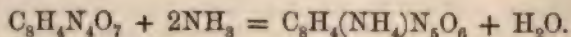


Parabanic acid, by taking up two molecules of water is transformed into oxalic acid and urea—



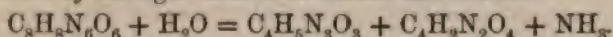
It is thus shown that the products of the oxydation of uric acid are urea, carbonic anhydride, and oxalic acid; of these the latter is easily transformed into carbonic anhydride and water by the accession of an atom of oxygen. These reactions have given rise to the hypothesis that uric acid is a product of the animal economy which might, or ought to have been, oxydised into urea, carbonic acid, and water, but which has escaped such oxydation. The hypothesis involves another, namely, that all urea in the urine was at a stage immediately previous to its formation in the form of uric acid. As a certain degree of probability, and with relation to the chemical process which determines gout, great importance attaches to these hypotheses, they should be further investigated.

Uric acid, when dissolved in dilute nitric acid, yields alloxantine, $C_8H_4N_4O_7 + 3H_2O$, distinguished by a purple reaction when ammonia is added to its warm solution, or ammonia gas is passed over a quantity of the dry substance kept hot in the water-bath. The purple product is murexide, or purpurate of ammonium—

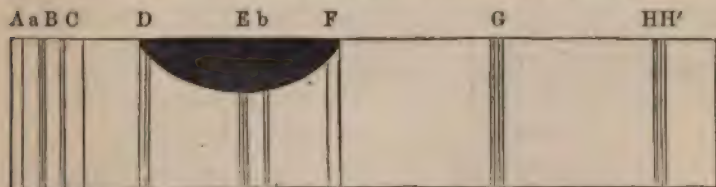


Murexide was first obtained by Scheele, and analysed by Prout, who declared it to be the ammonium salt of purpuric acid. This opinion was frequently called in question by chemists, as the acid could not be obtained in the free state. The researches of Beilstein ("Ann. Chem." 107 (1858) 176)

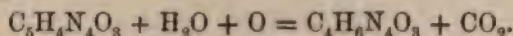
have, however, proved that murexide is really acid ammonium purpurate, and that purpuric acid, although of considerable stability in its compounds, is decomposed in the moment of its liberation by stronger acids into uramil and alloxan—



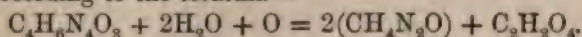
This reaction furnishes a test by which small quantities of uric acid can be recognised. When it is desired to test for uric acid small quantities of material obtained from organic mixtures, certain precautions are requisite to ensure the integrity of the test. The first of them is to purify the substance to be tested from colouring matters, which also yield fallacious, red or reddish reactions under the action of dilute nitric acid. If a small quantity of the purified matter is placed in a porcelain dish with a few drops of nitric acid, and after solution evaporated to dryness on the water-bath, a residue is obtained which assumes a purple-red colour descending from the sides towards the middle of the dish. A drop of water will effect solution of the residue, all colour disappearing for the time. Renewed evaporation will again produce the colour. Care must be taken not to add an excess of ammonia to the residue, as that quickly destroys the colour or prevents its appearance. When only a small amount of residue remains it is best to merely moisten it with a trace of water, and blow a little ammonia vapour upon it, when, if it be or contain alloxantine, the purple colour of the murexide will at once appear. The solution can be further identified by its spectrum.



On making uric acid and water into a pap, and gradually adding plumbic peroxide, and keeping the mixture near the boiling-point, the lead is transformed into oxalate, and carbonate, carbonic acid is evolved with effervescence, and the filtered fluid, on cooling, deposits crystals of allantoin; the mother-liquor yields urea. The reaction consists, in the first instance, in the transformation of uric acid into allantoin, according to the equation—



Some of the allantoin is further oxydised into urea and oxalic acid, according to the formula—

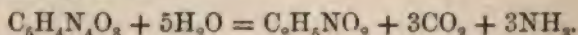


It will be seen that the last products of this reaction are the

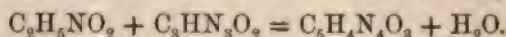
same as those of the oxydation by concentrated nitric acid, namely, urea, oxalic, and carbonic acid, but that the succession in which they are obtained is different. Both reactions show that there is one atom of carbon in uric acid less intimately combined, and more accessible to oxygen than the other four atoms; in the reaction with lead peroxyde this atom is oxydised and split off at once; but in the reaction with nitric acid it remains attached to the rest which forms alloxan, and is only detached from this by a secondary oxydation.

Allantoine derives its name from its having originally been discovered in the liquid which surrounds the fœtus *in utero* of horned cattle, and was supposed to represent the fluid of the allantoic membrane, but is actually that of the amniotic sac as well. It seems to be there as the product of the urinary excretion of the fœtus; for after birth it is still found in the urine of the sucking calf, and is only gradually displaced by the ordinary constituents of the urine of adult cows.

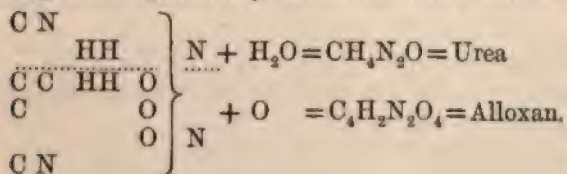
Uric acid is not decomposed by boiling, even for a long time, with concentrated hydrochloric acid. But when dry uric acid is heated in sealed tubes with hydriodic or hydrochloric acid saturated in the cold to 160° and 170°, it takes up the elements of water and is decomposed into ammonia, glykocoll, and free carbonic anhydride—



If we consider the elements of glykocoll to stand in some particularly near relation to each other in the uric acid, then the rest of $\text{C}_5\text{N}_3\text{O}$ may be considered as the complement. A body of the composition $\text{C}_3\text{HN}_3\text{O}_2$, might on combining with glykocoll under elimination of an atom of water form uric acid, thus—



Notwithstanding these remarkable reactions the chemical constitution of uric acid is not yet certainly evolved. If it stood in the relation to xanthine and hypoxanthine indicated by the reactions and composition of these bodies, it might be considered as a double ammonium base, having the properties of an acid. In this case hydrogen might be considered to be replaced by the radicals cyanogen, glycolyl, carboxyl, oxygen, all of which might be expressed by the structure formula—



Salts of Uric Acid; Urates.—Uric acid being a dibasic acid forms two kinds of salts, neutral and acid ones. The neutral salts contain two atoms of a monodynamic metal or one atom of a didynamic metal, in place of two atoms of hydrogen. Thus neutral sodic urate is $C_5H_2Na_2N_4O_3 + H_2O$, neutral calcic urate $C_5H_2CaN_4O_3 + H_2O$. These salts are very unstable, and are decomposed by carbonic acid. The acid urates are permanent salts, and contain one atom of a monodynamic metal in the place of one hydrogen of the acid. They contain half a molecule of water upon every dynamicity of metal, consequently the sodium salt has the formula $2(C_5H_3NaN_4O_3) + H_2O$. But the salts of the didynamic metals have the formula represented by the calcium salt $C_{10}H_6CaN_8O_6 + H_2O$.

Ammonic Urate.— $C_5H_3(NH_4)N_4O_3$ is always produced when uric acid and ammonia meet each other. When pure and dry it is a white amorphous mass, perfectly soluble in water, one part, however, requiring for solution 1608 parts of water at 15° . It may be obtained in small delicate needles by treating uric acid in boiling water with an excess of ammonia, or by dissolving uric acid in a warm solution of phosphate of soda and ammonia, and allowing the crystals to separate by rest. In the latter case the needles are united in groups, irregular or regular, presenting a star-like arrangement of rays emanating from a solid globe. The presence of urine, chloride of ammonium, sodium, or acetate of ammonium prevents this form of crystallisation. When crystallising out of a solution in ammonia, it forms roundish, oval, or dumb-bell-like masses of a radiated structure and polarising properties. When appearing as a precipitate in ammoniacal urine, it forms very slender dumb-bells, which were first described and figured by Prout ("Stomach and Urinary Diseases," 3d edit. Pl. I. figs. 1 and 4). This physician also found that a peculiar kind of urinary calculus sometimes met with consists of ammonic urate.

Acid Sodic Urate.— $2(C_5H_3NaN_4O_3) + H_2O$ is obtained by dissolving uric acid in caustic soda, and precipitating it by a current of carbonic anhydride; by mixing a boiling solution of uric acid in caustic soda with sodic bicarbonate, or by digesting uric acid in a hot solution of common sodic phosphate. By the first preparation, or by spontaneous evaporation of a saturated solution, the salt is obtained in spherical masses and granules. The second and third mode of preparing yield it in the form of delicate needles, which combine to form stars and tufts. It occurs in the urine dissolved, and as a sediment in the blood during gout, and in gouty concretions. It is soluble in 123 to 125 parts of boiling water, and requires 1100 to 1200 parts of water of 15° . The solution is neutral, and does not absorb carbonic acid; a precipitate is produced in it by the bicarbonates of alkalies, and by the salts of baryum, lead, and silver.

Sodic Quadriurate, $C_5H_3NaN_4O_3 + C_5H_4N_4O_3$.—This salt occurs naturally in deposits from healthy urine, and may be prepared artificially as follows:—Pure uric acid is dissolved in soda-ley, and acetic acid is added to the diluted solution until it has a feebly acid reaction. The precipitate which forms has the above composition. The compound may also be obtained by dissolving uric acid in a heated solution of common sodic phosphate, but is then mixed with common acid urate. When to the solution of uric acid in sodic phosphate varying amounts of hippuric acid are added, sediments are obtained after several hours' standing, which may be either uric acid, or sodic quadriurate, or a mixture of both. The sodic quadriurate is amorphous. When thrown on a filter and washed with water, the substance remaining on the filter is changed into a mass of crystals, consisting of pure uric acid. The filtrate contains acid sodic urate in solution. This decomposition of the quadriurate in acid urate and free uric acid is effected quicker by boiling with water. The compound bears washing with methylated spirit without undergoing change.

Acid Potassic Urate, $2(C_5H_3KN_4O_3) + H_2O$, is obtained by the same process as the sodic salt, best by treating with carbonic acid the solution of uric acid in caustic potash. It then appears in granules. When these are dissolved in boiling water they do not reappear on cooling, but flakes are deposited in their stead, which, after drying, form an amorphous mass. The salt requires for solution from 70 to 80 parts of boiling, and from 780 to 800 parts of water of 20° . It is insoluble in alcohol and ether, and does not, unlike the urate with two atoms of potassium, absorb carbonic acid. Its watery solution has a neutral reaction, no taste, and is precipitated by ammoniac chloride, the alkaline bicarbonates, and solution of baryum, lead, and silver.

Potassic Quadriurate, $C_5H_3KN_4O_3 + C_5H_4N_4O_3$, occurs in healthy urine as a deposit, and may be prepared by dissolving uric acid in potash, and adding acetic acid until the liquid is slightly acid. On standing, an amorphous precipitate falls, which is soluble on heating, and contains no free uric acid. But when it is washed with water even once, it is decomposed, uric acid in a crystallised state remaining on the filter, and acid urate passing through the filter dissolved in the water. The same decomposition is effected by boiling with water, and in so complete a manner that the crystals of uric acid, separated after cooling, contain no trace of potash. The salt is not decomposed by washing with alcohol.

Acid Calcic Urate, $C_{10}H_6CaN_8O_6 + H_2O$, occurs occasionally in small quantities in the urine, in sediments and concretions, particularly the gouty tumours near joints. It can be obtained by mixing a solution of calcic chloride with a boiling solution of potassic or sodic urate, when calcic urate falls down as an amorphous precipitate. If the urate employed is a little

alkaline, warty groups of needles are sometimes obtained. The salt requires 603 parts of cold and 276 parts of boiling water for solution. Its solubility is, however, increased by the presence of a small amount of potassic chloride.

Acid Baric Urate has the same constitution as the calcic salt, but is much less soluble in water. It is sometimes produced in chemical operations upon the urine for the isolation of other substances, *e.g.*, the alkaloids by the phosphomolybdic acid process.

The *urates of the heavy metals* are mostly amorphous insoluble precipitates. The silver compound is quickly decomposed by separation of silver. A compound of uric acid with copper, probably cuprous urate, is obtained by mixing a hot solution of sodic urate with a hot solution of Fehling's copper test, and heating gently for a short time. A white precipitate is the compound in question. It is very little soluble in boiling ley or water, and when treated with hot hydrochloric acid immediately yields crystallised uric acid, while copper goes into solution, and gradually assumes a deeper colour by oxydation. A dilute alkaline solution of urate when boiled for some time with excess of Fehling's solution is entirely destroyed, while red suboxyde of copper is deposited. It is therefore clear that in the foregoing formation of a cuprous salt the reduction of the oxyde is effected at the expense of a portion of the uric acid.

Amorphous Deposits of Urates in Healthy Urine.—In the urine of healthy men, who eat much meat, and drink little water, a deposit occurs with considerable regularity. It appears from the analyses of various inquirers (Heintz, "Müller's Archiv," 1845, p. 230; Scherer, "Canstatt's Jahresber.," f. 1849; Bence Jones, "Chem. Soc. Journ." 15, 201) that it has no constant composition, but is a mixture of different acid urates, which, by the influence of other substances contained in the urine, have lost their peculiar crystalline forms, and separate in an amorphous condition. In most analyses the potassic urate has been found to be present in larger quantity than either the ammoniac or the sodic salt. It has also been found that the uric acid contained in these deposits is sometimes larger in quantity than could be accounted for by the assumption of these deposits consisting of acid urates only, and that this excess of uric acid is held in combination by the acid urates, but so feebly that it is set free and assumes the crystallised state by mere washing with cold water. It may consequently be considered as certain that the deposits of amorphous urates may consist of acid urates simply, or contain varying proportions of hyperacid salts, namely, the quadri-urates described in the foregoing.

Qualitative Examination of Deposits of Urates in Healthy Urine.—The precipitate is allowed to settle, the clear urine poured off, and the sediment thrown on a filter, and washed with spirit of wine. When well washed it is put in a watch-glass, and

allowed to become dry at the temperature of the air. The precipitate must now be examined with the microscope, and if it contains uric acid crystals it is unserviceable for the inquiry relating to hyperacid salts or quadriurates. It almost always contains some oxalate of lime crystals, which do not sensibly interfere with the examination. But when it is desired to exclude them altogether, the deposit of urates must be redissolved by heating it in the urine from which it was originally deposited, the solution filtered, and the deposit allowed to form again. A portion of the deposit isolated as just described is diffused in water and boiled. If it dissolves entirely, acid urates only are present. Sometimes, however, it will be found to dissolve only partially, and to leave a considerable insoluble residue consisting entirely of uric acid, although no crystals of uric acid could be discovered in the original deposit. In these cases the deposit is clearly decomposed by boiling with water.

The filtered watery solution on cooling gives an amorphous precipitate, which is much increased in quantity by concentrating the solution. The precipitate is collected on a filter, washed, and dried. A portion of it burned leaves a strongly alkaline ash. Another part dissolved in water, and treated with hydrochloric acid, yields crystals of uric acid. A third portion treated with caustic potash evolves ammonia. The alkaline ash is mostly entirely soluble in water, and contains potash, recognised by the yellow precipitate with platinic chloride, and soda, colouring a blue gas—or spirit-flame strongly yellow. In other cases a portion of ash is insoluble in water, but dissolves in hydrochloric acid. This solution made alkaline with ammonia is treated with some oxalic acid. A white precipitate shows the presence of lime in the deposit. The filtrate from the oxalate in very rare cases gives a scanty precipitate on addition of sodic phosphate, showing the presence of a little magnesia.

Quantitative Determination of the Ingredients of Amorphous Deposits.—A quantity of deposit amounting to at least 1.5 gm. should be collected, washed with alcohol, dried, and weighed. It is decomposed by acetic acid, which separates calcic oxalate and uric acid. The calcic oxalate is extracted from the uric acid by hydrochloric acid; the uric acid is further purified by solution in potash and precipitation by hydrochloric acid, and then filtered, washed, dried, and weighed. The clear acetic acid solution is then mixed with hydrochloric acid, and after 24 hours' standing, filtered to separate colouring matter. The liquid is then evaporated to the smallest possible bulk, and precipitated by a solution of platinic chloride, and a mixture of absolute alcohol and ether. After 24 hours the precipitate is filtered off, washed with alcohol and ether, dried, and heated to redness; the platinum which remains is treated with dilute uric acid, and the weight of the platinum determined.

The hydrochloric acid solution which is filtered from the platinum is evaporated, and the potassium is precipitated by platinic chloride, washed with alcohol and ether, dried, and heated to redness; the residue is extracted with hydrochloric acid, washed, and the platinum determined. This gives the amount of potassium, and by deducting this from the amount of platinum previously found, a difference is found which gives the amount of ammonia present.

The liquid filtered from the first platinum precipitate is evaporated, and the residue burnt at a gentle heat. It is then boiled with hydrochloric acid, the solution decomposed by a few drops of sulphuric acid, evaporated to dryness, heated to redness, and weighed. From the amount of sodic sulphate found, the sodium is calculated. In cases where calcium or magnesium are present, this latter filtrate from the first platinum precipitate contains both the metals. They have then to be removed from the hydrochloric acid solution of the burnt residue by boiling it with ammonic carbonate and excess of ammonia. The filtrate, after evaporation, treatment with sulphuric acid, and ignition, yields the sodium in the form of sulphate. From the acetic acid solution of the mixed carbonates, the calcium is obtained as oxalate by precipitation with ammonic oxalate; the filtrate treated with sodic phosphate and excess of ammonia deposits any magnesium which it may contain after some standing. By analyses performed upon four different deposits, the following amounts of ingredients were found by Scherer:—

Uric acid,	82.89	80.02	81.31	82.89
Ammonia,	2.23	8.29	7.09	2.23
Potash,	2.04	1.38	2.80	2.04
Soda,	0.55	2.05	0.17	0.55
Lime,	0.56	0.34	0.26	0.55
Calcic phosphate, . .	0.37	2.72	0.57	...
Calcic oxalate, . .	0.33			
Colouring matter and loss,	11.03	5.20	7.86	11.74

By these analyses, the proportion of combined uric acid (supposed to be in the form of acid urate) to free is shown to be subject to great variations, as will be seen from the following calculation given by Bence Jones. In analysis

No. 1.			
Ammonia,	2.23	require of uric acid	13.61
Potash,	2.04	"	6.90
Soda,	0.55	"	2.94
Lime,	0.56	"	3.55
<hr/>			
Combined uric acid,			27.00
Free uric acid,			55.89
<hr/>			
Total uric acid found,			82.89

Hence combined is to free as 1 : 2.04.

URIC ACID.

No. 2.

Ammonia,	8.29	require of uric acid	50.60
Potash,	1.38	" "	4.66
Soda,	2.05	" "	10.96
Lime,	0.34	" "	2.15

Combined uric acid,	68.37
Free uric acid,	11.65

Total uric acid found, 80.02

Hence combined is to free as 1 : 0.17.

No. 3.

Ammonia,	7.09	require of uric acid	43.28
Potash,	2.80	" "	9.48
Soda,	0.17	" "	0.91
Lime,	0.26	" "	1.65

Combined uric acid,	55.32
Free uric acid,	25.99

Total uric acid found, 81.31

Hence combined is to free as 1 : 0.42.

No. 4.

Ammonia,	2.23	require of uric acid	13.61
Potash,	2.04	" "	6.90
Soda,	0.85	" "	2.94
Lime,	0.55	" "	3.49

Combined uric acid,	26.94
Free uric acid,	55.95

Total uric acid found, 82.89

Hence combined is to free as 1 : 2.08.

In three analyses given by Bence Jones, the following quantities of bases, combined and free uric acid, were found:—

No. 1.

Ammonium,	0.22	require \bar{U}	2.17
Potassium,	0.51	" "	2.16
Sodium,	0.18	" "	1.30

Combined uric acid,	5.63
Free uric acid,	9.61

Total uric acid found, 15.24

Hence combined is to free as 1 : 1.72.

No. 2.

Ammonium,	0.81	require \bar{U}	8.00
Potassium,	0.91	" "	3.84
Sodium,	0.43	" "	3.12

Combined uric acid,	14.96
Free uric acid,	6.96

Total uric acid found, 21.92

Hence combined is to free as 1 : 0.46.

No. 3.

Ammonium,	0.273	require	U	2.01
Potassium,	0.856	"	"	3.61
Sodium,	0.203	"	"	2.00
				<hr/>
Combined uric acid,				7.62
Free uric acid,				7.94
				<hr/>
Total uric acid found,				15.56
Hence combined is to free as 1 : 1.04.				

Experimental Comparison of various modes of determining the Quantity of Uric Acid contained in Urine.

It having lately been asserted that the various modes of determining uric acid, which were in use hitherto, did not yield more than from one-third to one-half of the uric acid actually contained in urine, the following trials were made:—

Exp. 1, 2, and 3 were made upon the same material.

Exp. 1. 350 c.c. of filtered urine were evaporated to an extract, and 3.5 c.c. of hydrochloric acid (of 1.16 sp. gr. containing about 32 per cent. of anhydric acid) added. After 48 hours' standing the precipitate was filtered off, washed, dried, and weighed. It was equal to 0.2520 grammes. The day's urine having been 1400 c.c. this would have yielded the unusual quantity of 1.008 grammes of uric acid for 24 hours. The precipitate being dark brown-red, and mostly amorphous, was likely to be very impure. It was therefore purified as follows:—It was dissolved in potash, which left no residue; it was then again precipitated by hydrochloric acid and washed with alcohol, which extracted colouring matter, that is the resinous mixture of uropittine and omicholic acid, and a few undeterminable microscopic needles. No hippuric acid could be discovered in the extract, either by the microscopic or by the nitric acid test. The precipitate of uric acid was crystallised in club-shaped hexagonal needles, which were homogeneous throughout, although yet reddish. It weighed 0.1582 grammes. The process of purification had therefore removed 0.0938 grammes of impurity. The physiological quantity of uric acid for the 24 hours was therefore 0.6328 grammes.

The impurities removed were mucus, of which there is always a quantity in the evaporated extract, phosphate of lime, which falls down in the extract, and redissolves in the caustic potash, remaining in solution together with much mucus in the last hydrochloric acid mother-liquid, and colouring matter.

Exp. 2. 350 c.c. of the same urine, filtered, were treated with 3.5 c.c. of nitric acid (of 1.4 sp. gr. containing 60 per cent. of anhydric acid). The deposit of uric acid obtained after 24 hours was in particularly large and well-defined crystals, and weighed dry 0.0875 grammes, or a little more than one-half of the purified

uric acid obtained in Exp. 1. It would have yielded as the uric acid of 24 hours 0.3400 grammes.

Exp. 3. 350 c.c. of the same urine, filtered and mixed with 3.5 c.c. of hydrochloric acid, after 48 hours yielded 0.0835 grammes of uric acid. This would have yielded as the physiological amount of uric acid 0.3340 grammes.

Exp. 4. The above experiments having taught that in order to extract the whole amount of uric acid from urine it must be evaporated, and the precipitate obtained by acid be purified, the urine of a healthy man, *æt.* 36, passed during 24 hours, from July 20, 9 P.M., to July 21, 9 P.M., total 1870 c.c. was filtered, evaporated on water-bath to an extract, and mixed with its bulk of alcohol. The extract was mixed with alcohol and one drop of hydrochloric acid. The deposit obtained after 24 hours was separated. The filtered alcoholic solution on the addition of hydrochloric acid yielded no uric acid. All the uric acid was in the deposit, together with phosphates and mucus. It was gently heated with caustic potash until all ammonia had been driven off. It was then filtered from the residue of phosphate of lime. Filtrate and washings were concentrated, mixed with absolute alcohol, and treated with hydrochloric acid until the fluid had a strongly acid reaction. However, as the deposit again contained phosphates, which are largely soluble in caustic potash, and easily crystallise from hydrochloric acid solution in the presence of alcohol, it was mixed with water, treated with some hydrochloric acid, filtered, washed, and dried. This slightly coloured very pure uric acid weighed 0.3885 grammes (5.99844, say 6 grains).

Exp. 5. Urine of 24 hours, July 21, 9 P.M. to July 22, 9 P.M., 1350 c.c. filtered, evaporated on water-bath and treated in all respects as the urine in Exp. 4, yielded uric acid 0.3710 grammes.

Exp. 6. Urine of 24 hours, July 22 to 23, 1425 c.c. filtered and evaporated on water-bath. Uric acid = 0.3412 grammes.

Exp. 7. Urine of 24 hours, July 23 to 24, 1100 c.c. filtered, evaporated to extract and 11 c.c. of hydrochloric acid and 80 c.c. of alcohol of 92 per cent. added. The precipitate contained a large amount of phosphatic earths. These were extracted by dilute hydrochloric acid. The residue dissolved in caustic potash and precipitated by hydrochloric acid weighed 0.4295 grammes.

Exp. 8. Urine of July 24 to 25, 24 hours, 1550 c.c. filtered, evaporated, 15.5 c.c. of HCl and 100 c.c. of alcohol added, and deposit treated as in Exp. 7, yielded 0.2820 grammes of uric acid.

Exp. 9. Urine of July 25 to 26, 24 hours, 950 c.c. 9.3 c.c. HCl added and 90 c.c. of alcohol, yielded \bar{U} = 0.4262 grammes.

Exp. 10. Urine of July 26 to 27, 24 hours, 1735. Evaporated and treated as in Exp. 7, yielded \bar{U} 0.5685 grammes.

Exp. 11. 300 c.c. of urine, July 28, total 1650 c.c., were filtered, evaporated to extract, had 3 c.c. of HCl added, and were allowed to stand 24 hours. The precipitate was very red and

weighed 0·2250 grammes. It contained the impurities described in Exp. 1.

Exp. 12. 300 c.c. of the same urine as that used in Exp. 11 were evaporated to extract, mixed with 30 c.c. of alcohol, the white deposit was extracted with potash, and the potash solution precipitated by HCl. It yielded uric acid, nearly colourless, 0·1100 grammes. More than one-half of the deposit obtained in Exp. 11 had evidently been impurity.

In order to avoid the sources of error arising from operations with small quantities, the following series of twenty experiments was made, to determine the amount of uric acid excreted by a healthy man, the same as in the above twelve experiments. The urine was collected on twenty successive days with the greatest regard to accuracy. The number of c.c. is stated in the first column. The uric acid was determined in either portions or the total quantity of each day by evaporation to an extract, the addition of 1 per cent. of HCl and filtration after long standing. The deposits contained phosphates and mucus and colouring matters. To purify them they were washed with much water heated with caustic potash, filtered from the mucus, and after the addition of alcohol reprecipitated by HCl. The precipitate was treated with some HCl to extract a small quantity of earths, and then with some alcohol. The dried residue, fawn-coloured crystallised uric acid, was weighed. It will be seen that the result confirms the average of Exp. 4 to 10:—

No. of Experiments.	Total Urine excreted in 24 hours.	Amount evaporated for analysis.	Uric Acid calculated for 24 hours.
13	1,370 c.c.	500 c.c.	0·2504 grm.
14	1,580 "	500 "	0·2888 "
15	1,720 "	500 "	0·3144 "
16	1,600 "	500 "	0·2924 "
17	1,525 "	1,525 "	0·2787 "
18	1,500 "	1,345 "	0·2742 "
19	1,470 "	1,470 "	0·2687 "
20	2,300 "	2,150 "	0·4204 "
21	1,420 "	1,420 "	0·2595 "
22	1,670 "	1,670 "	0·3052 "
23	2,200 "	2,200 "	0·4021 "
24	1,600 "	1,600 "	0·2924 "
25	2,200 "	2,200 "	0·4021 "
26	1,050 "	800 "	0·1919 "
27	1,450 "	1,450 "	0·2650 "
28	1,260 "	1,260 "	0·2303 "
29	1,860 "	1,860 "	0·3400 "
30	1,850 "	1,850 "	0·3381 "
31	1,600 "	1,600 "	0·2924 "
32	1,780 "	1,780 "	0·3253 "
Total 20 days.	33,005 c.c.	28,180 c.c.	

The 28,180 c.c. of urine analysed yielded 5.1525 gm. of uric acid, corresponding to 6.0324 gm. in 33,005 c.c.

One c.c. of urine, therefore, contained on an average 0.0001828 gm. of uric acid.

The average quantity of urine excreted during each of the twenty days was 1650 c.c.

Consequently, the average of one day's uric acid is 0.3016 gm. or 4.6567 grains.

If this result is compared with the results of the analyses performed on the urine of single but entire days, it is found that the latter yielded figures the average of which is 25 per cent. higher than the average of the twenty days analysed together, thus:—

Number of Experiments.	Total of Urine.	Uric Acid obtained.
4	1,870 c.c.	0.3885 gm.
5	1,350 "	0.3710 "
6	1,425 "	0.3412 "
7	1,100 "	0.4295 "
8	1,550 "	0.2820 "
9	930 "	0.4262 "
10	1,735 "	0.5685 "
Total, 7	9,960 c.c.	2,8069 gm.

Mean of urine per day, 1422 c.c.

Mean of uric acid per day, 0.4 gm.

When fractions of days' excretions are analysed, the figures obtained for uric acid are still higher.

The smaller the quantities of reputed uric acid manipulated upon are, the greater is the amount of impurity that remains adhering to them.

The above analyses clearly prove that by the most reliable proceedings no more than 0.35 gm. of uric acid could be obtained from the urine of a healthy man during each average day of a period of 27 days (of which 20 were separated from seven by an interval of time).

Results:—

1. Concerning the methods of analysis, it is proved that none of those hitherto in use give either the actual amount of uric acid contained in urine, or a pure product which may be taken into account as uric acid. In particular:—

a. The methods employing the addition of an acid only to a measured quantity of urine do not obtain the whole of the acid contained, yet with the uric acid they precipitate a certain amount of decomposed urochrome.

b. The methods which employ concentration of the urine to an extract, and the addition of an acid, obtain the whole amount

of uric acid with a considerable admixture of decomposed urochrome (of which uromelanine is insoluble in alcohol), with phosphates and urates, particularly urate of soda and ammonia, and mucus.

c. The methods which employ inspissation and extraction of the deposit with alcohol, then treatment with acids for the extraction of phosphates, obtain relatively the most correct results, as the product is least coloured, and contains the smallest amount of impurity, while no uric acid is lost; yet there remains so much of mucus, ammonia, and phosphate with the uric acid that the result is unreliable.

d. The method which on all grounds and in practice gives the most satisfactory results is the following:—The urine having been evaporated to an extract (not less than one day's urine should be analysed at a time), is treated with four or five times its volume of strong alcohol (90 per cent.) well shaken, and allowed to stand 24 hours. The fluid is filtered off, and the deposit washed with alcohol until colourless. This deposit is now treated with water and hydrochloric acid for the extraction of phosphates. The residue of uric acid is washed and dissolved in some caustic potash, warmed until all ammonia is gone, and reprecipitated by the cautious addition of hydrochloric acid until the fluid, which should be still warm, has an acid reaction. The vessel is then allowed to stand in a cool place for 24 hours, when the uric acid may be isolated and weighed in the usual manner.

2. Concerning the physiological quantity of uric acid excreted by a healthy man, it is shown to be about 0.35 grammes in 24 hours on an average. This result, and the consideration of the various modes of analysis and sources of error in them, leads to the belief that the old method of analysis by hydrochloric acid alone was, perhaps, less misleading than the mode employing evaporation and hydrochloric acid.

Amount of Uric Acid discharged during 24 hours.—Various researches instituted upon healthy adult males have shown that they may excrete quantities of uric acid varying from an average of 0.3 gm. per 24 hours in one individual to 1.0 gm. in another. But in feeble persons the quantities may be much lower, and sink to a minimum of 0.02 gm. in 24 hours. In the urine of some feeble and badly-fed persons no uric acid at all can sometimes be found. It is, therefore, not improbable that the amount of uric acid excreted by given individuals may stand in a certain proportion to the nature and quantity of the food taken, and to the organic changes of the body. For this reason quantitative determinations of the amounts excreted by different individuals of all ages and both sexes have a certain value, provided that the circumstances of the individual, the ingesta, and the organic

changes are taken into consideration. The normal constants of uric acid are, however, not yet ascertained with the desirable precision, and particularly upon females and children a large number of observations will yet be required before they can be employed as the bases for pathological conclusions.

The fluctuations of uric acid in health are more considerable than those of other well-known constituents of the urine; they occur in the same individual within short periods of time. It is, therefore, at present almost impossible to say in any given case whether the quantity of uric acid excreted by an individual in a given time is below or above the average, and can in either extremity be an effect of pathological conditions.

If the mean quantity of urea discharged by healthy men in 24 hours is 33 grm., and that of uric acid 0.54 grm., the proportion of urea to that of uric acid is about 1,000 to 16.

Pathological Changes in the Quantity of Uric Acid Discharged during Twenty-Four Hours.

We here consider what proximate conditions of the system a rise or fall in the quantity of uric acid beyond the normal limits is likely to indicate. A deficiency may be due to a diminished production in the system, as in anæmia, or to retention, as in certain stages of gout and rheumatism. It is at least questionable whether the retention is *always* due to diseased action of the kidney. Any disease, however, which interferes with the secreting power of the kidney by changing its structure, such as Bright's disease, is certain to cause retention of uric acid in the blood, in proportion to the retention of the other constituents of urine. Scarlatina seems to make an exception. I have certainly found that in some cases of this disease, where uric acid is frequently present in excess from the beginning, so as to be precipitated in a cloud by the addition of an acid, the amount of uric acid does not decrease parallel to the fall of urea, when, with albuminous urine, dropsy appears; but it seems to be normal in amount, even at a time when the amount of urea is about half the normal average. Many observations will, however, be necessary to decide whether such a process is the rule or the exception.

An excess of uric acid may be due to excessive production in the body, particularly when the increased excretion lasts for a certain time. It may, however, be owing to the discharge of accumulated uric acid, after retention in the blood. In both cases the symptoms accompanying or preceding the excessive excretion must be our guides in distinguishing between these conditions.

As a general rule, *i.e.*, one liable to exceptions, it may be assumed that an excessive production of uric acid accompanies

an excess in the production of urea. In inflammatory diseases and certain other febrile diseases, an increased amount of uric acid is met with.

The following observations of Becquerel are entitled to attention, as referring to the total quantities of uric acid discharged in 24 hours:—

Healthy urine (B's average),	8.1 grains.
Chlorosis, five cases,	min. 1.8 max. 6.0 "
Pulmonary emphysema, ext. dyspnoea,	4.9 "
Phthisis, tubercles softened,	9.1 "
" three days before death,	9.8 "
Morbus cordis, with icterus,	9.82 "
Acute hepatitis, with icterus,	11.18 "
Icterus,	17.75 "
Milk fever,	19.0 "

So the quantities found in these cases (excepting only the two last ones) are neither higher nor lower than the average quantities obtained in perfect health. In the case of icterus and milk fever, however, the amount of uric acid is evidently increased.

Amorphous Deposits of Urates in Diseases—Urate of Ammonia.—The urate of ammonium in some rare instances occurs by itself, mixed only with very small traces of the urates of fixed bases. It is probable that in those cases the urine always contains an excess of ammonia in the form of carbonate, which is due perhaps to a partial decomposition of urea. As all urates in the presence of ammonium salts transform into urate of ammonium, no other urate besides that of ammonium can exist for any length of time in ammoniacal urine. It is for this reason also that the urates of the alkalies or earths, or uric acid deposited from acid urine, are soon transformed into ammonic urate when the decomposition of the urea has produced a sufficient amount of volatile alkali.

As a general rule, urate of ammonium, when occurring as a deposit, forms a granular, perfectly amorphous precipitate. But in some descriptions of alkaline urine, or urine which has become ammoniacal without the body, it forms roundish, oval, or dumb-bell like masses, like the forms which crystallise from the solution of pure urate in caustic ammonia.

When appearing as a precipitate in ammoniacal urine, it forms very slender dumb-bells. The ammonic urate deposit occurring before emission is of particular importance, as it gives rise to a peculiar concretion, the ammonic urate calculus.

Deposits of Mixed Urates Occurring after Emission.—To the naked eye these deposits appear as a subtle powder, varying in colour from absolute whiteness, through rose-colour, pink, brick-red, purple and brownish-red. These colours are best observed after

the deposit is collected on a filter. The colours of urates generally are caused by the adhesion to their particles of varying quantities of an abnormal colouring matter—urerythrine. For this they have so great an attraction that they may be used for separating urerythrine from deeply-coloured urine; repeated quantities of urates are dissolved in the urine with the aid of a gentle heat; on cooling they are reprecipitated, carrying the urerythrine with them.

The brick-red or pale fawn-coloured so-called lateritious deposit occurring so commonly in the urine in febrile diseases is almost always a mixture of the urates of ammonium, sodium, potassium, calcium, and magnesium. When burnt on platinum-foil, it leaves a white ash containing the bases. The chemical characters of these substances are better marked than the microscopic, and should be investigated in detail for clinical purposes. These deposits are rarely observed in urine before it has cooled, and readily disappear when the urine containing them is raised to the temperature at which it left the body. They are soluble in ammonia and potash, and from these solutions uric acid is precipitated by acetic acid. When such a sediment after isolation is brought into contact with acetic or hydrochloric acid it is slowly transformed into uric acid crystals, the bases entering into combination with the acid, and forming soluble salts. The dry deposits give with nitric acid the characteristic reaction of murexide. The mode of analysing these deposits is the same as that prescribed for the deposits from normal urine. The extraction of the urerythrine will be found described under the chapter referring to that substance.

Indications of Deposits of Urates Occurring after Emission.

The deposits of mixed urates are so very common in the most varied conditions of health and disease, that it would be very difficult to name those conditions. The attempt to define the characters of urine depositing urates must be futile, because there is almost no description of urine that may not deposit them. Whether acid or alkaline, of high or low specific gravity, containing much or little urea and colouring matter, urine will, under certain circumstances, deposit urates. Whether occurring in the body or out of the body after emission, the conditions of the deposit are identical; there is not a sufficient quantity of water present to hold all the urates in solution at a certain temperature. The urine, therefore, after being saturated with the urates, deposits the excess; by the addition of water, or urine not saturated with urates, this excess may, under most circumstances, be dissolved. By concentration of urine, a deposit of urates may be produced.

As the only indication of a deposit of urates is, therefore, that

the urine containing it is, at that temperature, saturated with them; and as this may occur after strong physical exercise, after abstinence from liquids, or in a fever, this indication in itself does not point to any specific pathological condition. The amount of the urates may be the ordinary one, though there be a deposit. The indication of a deposit of urates becomes of importance only when considered with relation to the total quantity of urine and dissolved urates discharged in 24 hours; with this view we have to distinguish two different cases.

a. If the bulk of the urine for 24 hours is the normal average, and if a sediment of urates continues to exist in that urine, it is tolerably certain that an absolute excess of urates is present.

b. If, on the other hand, the urine for 24 hours is below the average, a deposit may possibly be, and in most cases is, due to saturation only. The easiest process of ascertaining this, for ordinary practical purposes at least, is to dilute the urine with water to its average bulk, and to shake it well. If the deposit does not entirely dissolve, an excess of urates is present. If crystals of uric acid are liberated after a short time, quadriurates may be assumed to be present. The safest proceeding, however, is to ascertain the whole amount of uric acid secreted in 24 hours.

If the presence of a deposit of urates be taken as an indication of the saturation of urine by these salts, and if the latter be assumed ordinarily to be of the usual amount, deposits of that kind become more valuable as signs of a diminished secretion of water by the kidneys than of any other symptom. As the appearance of a deposit of urates is always accompanied by morbid sensations and objective symptoms, in the healthy by thirst at least, if by nothing more the conclusion is simple enough. *The individual whose urine has deposited the urates does not drink water enough, and must drink more, and must drink so much that the urine, at the ordinary temperature of the air, shall remain clear.* Of course, in some cases this will be neither possible nor advisable; but in most cases of acute and febrile diseases it should be a plan of treatment. I have certainly seen it attended by beneficial results in many cases; I have also observed want of water in the system to be a source of illness.

Deposits of Urates Occurring in the Urinary Passages.

On an average 20 calculi out of 230, or 8·69 per cent., present nuclei of urates, and 37 more out of 230, or 16·08 per cent., contain a certain amount of urates in the form of layers or crusts. The urates, therefore, somehow or other, enter into the composition of 24·78 per cent., or almost one quarter of all calculi.

Practically it is important to distinguish two modes in which deposits of urates may be produced in the urinary passages.

a. A urine nearly or just saturated with the urates is secreted by the kidneys, and collected in the bladder. By the endosmotic activity of the veins and lymphatic vessels of the bladder, a farther concentration of the urine is brought about, in consequence of which a certain amount of the urates passes out of solution, and forms a precipitate. These cases may be of rare occurrence, as is generally believed; or they may be overlooked, and the deposit may be taken for an ordinary deposit by cooling. It is just possible that the following case might have escaped my observation, but for the retention of urine accompanying the deposit in the bladder, making necessary the use of the catheter. The turbid urine, which escaped by the instrument, afforded ocular proof that the deposit had been formed in the bladder.

OBSERVATION.—R. G.—, *et.* 2, a delicate girl, had been for some time indisposed, and been troubled with thread-worms, which being removed for a time by the aid of *santonine* in oil, reappeared again after a time. On the 7th of September 1856 I was requested to see the child. For the last fortnight her parents had perceived her to be unusually quick of perception. Some days since she began to complain, and on the 5th felt so ill that she wanted to lie down. On the 6th a rash, characterising typhoid fever, made its appearance.

7th.—The child is giddy and wants to lie down. She is light-headed, almost fainting when raised, and complains of severe headache, frequently taking her head between her hands, and uttering exclamations expressive of the pain. She sleeps very little, being awake the greater part of the night. She has no appetite, but is very thirsty; her lips are dry and peeling; her tongue is covered with a thick fur in the middle, red at the sides and point, but moist all over. Since the last motion, two days ago, which contained many worms, the bowels have been confined. The abdomen is soft, not tympanitic. The pulse is very quick and hard. The skin is hot, generally pale, but covered with an eruption of the exact form of flea-bites, namely, a purple spot, of the size of the circumference of a pin's head, surrounded with a halo of a fainter purple colour. The spots do not disappear on pressure. I gave her a scruple of the syrup of iodide of iron three times a day. Of a mixture of two ounces of olive oil, half an ounce of castor oil, and six grains of *santonine*, she took two teaspoonfuls at once, and one teaspoonful every hour. It required half the oil to produce a dark, moulded motion.

8th.—Continues much the same. The spots have in some degree lost their halo. In the evening, the girl being sleepless and wandering, she began to squint.

9th.—The exanthema remains on the skin, and the spots have got larger. The child is very feverish. The urine passed yesterday is acid, reddish-yellow, contains much mucus, some epithelial casts from the tubuli of the kidneys, and deposits a granular sediment of urates. A drop of the urine placed between two slips of glass soon crystallises into a mass of crystals. After deposition of the small amount of surplus urates, the specific gravity of the urine is 1025, very high for a child of that age.

10th.—The spots get smaller, and lose their halo. They now do disappear by pressure, and return after it. The tongue is getting cleaner from the sides. She only passed a small quantity of urine once in the course of that day, with a motion of the bowels. She squints when excited.

11th.—The spots continue to get paler. The tongue is cleaning. The condition of the abdomen, contrasted with its soft state five days ago, shows dis-

tension. Ocular inspection and percussion show the collection of urine in the bladder, from which nothing had passed since yesterday. A warm poultice put over the abdomen and vulva, and a warm bath, not being of any avail in relaxing the sphincter of the bladder, the catheter was applied, and about eight ounces of urine, mixed with a white deposit, in flakes, escaped by the instrument.

It was the urine of two days, mixed with a copious deposit, which, on standing, settled to the bottom of the vessel. The urine now appeared of a reddish-yellow colour and of acid reaction. In a specimen, mixed with half its bulk of nitric acid, nitrate of urea crystallised on standing. The colour then became deep red. Hydrochloric acid, when added in sufficient quantity, at first coloured the urine dark blue, nearly black; but this colour after two or three hours transformed into dark cherry-red. A deposit of indigo did not therefore take place, though the reaction was indicative of its formation. The urine became black on the admixture of sulphuric acid. The specific gravity of the urine was 1025.

The deposit was white, and consisted of urates in dumb-bells, globules, and irregular agglomerations, mostly covered with spinous masses of the most varied, fanciful, and irregular description. Some of the globular masses were so large that they could be distinguished with the naked eye; and under the microscope, bristled with spinous masses. That the spines were urates was evidenced by their solubility in water; a deposit when washed on the filter with water, dissolved entirely, leaving no residue. By the influence of an acid, the urate was transformed into ovoid crystals of uric acid.

12th.—The catheterism of yesterday was followed by great relief, and the child passed a little urine spontaneously soon after. But the retention continued; and on this day the catheter discharged four ounces of the same description of urine, with the same amount and quality of sediment as on the day before.

On three following days the urine had to be drawn with the catheter, showing each time the same characters and the same sediment.

On the 16th, the child passed urine spontaneously, still mixed with a deposit; but it consisted of granules and dumb-bells only, with short indications of spinous masses only. This lasted for two or three days, after which the urine became clear, and after standing twenty-four hours deposited ovoid crystals of uric acid. From this time the child recovered her strength rapidly; and, with the assistance of some quinine and iron, was soon much stronger and better looking than at any time before her illness.

From the 10th to the 20th the child had taken no medicine whatever, owing to the absence of any indication. This is perhaps in favour of the observation.

The practical considerations on this case are many in number; but most important are the questions on the causes of the deposit and of the retention. The deposit was perhaps due to concentration of the urine in the bladder after secretion from the kidneys. Urine nearly or perfectly saturated with the urates arrived in the bladder; there it was deprived of a certain amount of water, and a deposit of the nature described fell down. It is probable that the spinous hedgehog-like masses so irritated the mucous membrane of the urethra at the infundibulum as to cause spasmodic contraction of the sphincter. I have seen strangury caused by the passage of almost microscopical crystals of uric acid, and yet they were ovoid round bodies. A similar obser-

vation has been made by Prout ("Stomach and Urin. Dis." 3d edit. p. 202). This confirms my opinion on the cause of the retention. I will not, however, deny the influence which the nervous system may have had in the spasmodic action, seeing that there was spasm in other parts as well, namely, in the muscles of the eye. The spinous deposit appeared and disappeared simultaneously with the retention; and a deposit of a much less irritating shape was discharged before the retention set in and after it ceased.

The following passage from Prout (*loc. cit.* p. 203), referring to actual observations similar to the one just now related, suggests the probability that in some cases the urate of sodium deposit may close the urethra by forming a simple plug, and without any spasmodic action being perceptible.

"About this period of life (*viz.*, the age of 40), or later, we occasionally see in certain modifications of gouty constitution large quantities of the lithate of soda, perfectly white, deposited in the urine. This compound sometimes assumes the form of amorphous sediment, and renders the urine quite milky when passed; but I have seen it copiously secreted of the consistence of mortar, especially during the night; and in this case it is apt to collect into masses and block up the urethra, so as to occasion considerable difficulty in passing the urine. Such instances are very rare, and appear to be associated with organic disease of the kidneys, and perhaps other organs." Of this association, however, Prout has not given any proof in observation.

b. The second mode in which deposits of urates may be produced in the urinary passages is by the urine in the bladder undergoing alkaline fermentation.

Deposits of Uric Acid Occurring after Emission.—It has hitherto been believed that these deposits are caused by a peculiar change of the excreted urine, termed the acid fermentation. But there are so many cases of deposits of lithic acid occurring soon after emission, in which fermentation cannot be shown to have any share, that there must be other causes at work in the production of these peculiar matters. These causes we may seek in the manner in which quadriurates are decomposed by water. It is probable that a specimen of urine which is saturated with quadriurates at a certain temperature may be decomposed by the addition of water or dilute urine in the same manner as the quadriurate would have been decomposed by water had it been deposited. In this manner alone can we explain the frequently-made observation that the clear urine of healthy children deposits crystals of uric acid after a few hours' standing, without any urates being deposited or decomposition engendered taking the form of acid fermentation. In this manner we must also explain observations such as this: A man discharged urine in the morn-

ing which formed a deposit of lithates; he kept it in vessel, and added to it the urine which was passed during the day and evening. Next morning the entire amount of lithates had been decomposed, uric acid in crystals remaining undissolved, the acid urates dissolving. It was clearly ascertained that the deposit which formed after cooling consisted of urates only, and contained no uric acid, and no acid fermentation could be found to be present.

Urates, which when isolated are decomposed by water, are also occasionally entirely decomposed into free uric acid and soluble salts of the bases by standing in the urine from which they were deposited. This is perhaps due to the formation of some free acid from extractive matters under the influence of the oxygen of the air; the acid may be acetic, which is always a final product of the decomposition of urine; but it has never yet been proved to be lactic, as was supposed by Lehmann and Scherer. This production of acid by chemical change in the urine itself has been termed a fermentation; the process was surmised to be engendered by a peculiar change in the mucus derived from the surface of the urinary passages.

Deposits of Uric Acid Occurring after Emission—Hypothesis of Intravesical Acid Fermentation.—As the alkaline decomposition of urine, which ordinarily occurs after emission, and which is termed alkaline fermentation, may already take place in the body under certain circumstances, it has been thought possible that an acid fermentation analogous to the one alluded to in the previous paragraph might also occur in the urinary passages. The direct proof of the existence of such a process has not yet been given, but there are data which make its existence probable. Thus it has been observed that in certain cases, in which the urine soon after emission deposited crystallised uric acid, and in which this deposition was accompanied or preceded by an increase in the acidity of the urine determined by quantitative analysis, this process was the forerunner of the deposition of uric acid in the urinary organs. It was supposed that different pathological conditions of the body might influence the mucus of the urinary passages in such a manner as to cause it to become a ferment, and that when once so predisposed its action upon the materials capable of furnishing acids was only a question of time; that therefore it could decompose the extractives within the body, and cause the precipitation of uric acid if the secretion remained in the bladder for a sufficient length of time, but that under favourable conditions, particularly of temperature, it could produce the same result out of the body. If there is really such a process of acid fermentation, and if it really not rarely precedes deposits of uric acid within the organs, then it is highly probable that a process analogous to the fermentation out

of the body may also take place within it. Of course, the effect produced by the acids created by fermentation will be materially influenced by the degree of acidity which the urine possesses on leaving the kidneys. But all these considerations must now be critically sifted by means of the information relating to quadriurates; for in these compounds there is a faculty of producing uric acid deposits by the conditions described which is far greater than that of any fermentation, if, indeed, the existence of quadriurates themselves in some few cases may not be due to fermentation.

According to the fermentation hypothesis, therefore, the conditions which precipitate uric acid within the urinary organs are the presence of an acid urine, in contact with a mucous membrane or its mucus, which is in an abnormal state, and acts as a ferment, decomposes extractives, produces more free acid than belongs to urine normally, and thereby precipitates uric acid.

Hypothesis of the Decomposition of Tetraurates.—The tetraurates also deposit uric acid immediately after emission, apparently as an effect of mere cooling. They also deposit uric acid by contact with water, and immediately by contact with acids. We have, therefore, in their existence a number of conditions for the deposition of intraorganic uric acid. Once formed and dissolved in urine in the urinary organ, they may deposit uric acid by the mere effect of time, by the effect of more dilute watery urine becoming mixed with the concentrated, or by the effect of more acid urine becoming mixed with the less acid urine.

Hypothesis of the Unequal Secretion by Different Pyramids in Kidney Disease.—It is frequently observed in kidney disease that the several pyramids are very unequally affected; that one is entirely destroyed, another actively invaded by disease, and a third almost healthy. It may be supposed that the pyramid just invaded, but still capable of secreting, will produce a urine differing in composition from the urine produced by the healthy pyramid. Two different secretions would therefore meet in the pelvis of the kidney and react upon each other. Now, if one produced a concentrated urine containing quadriurates, and the other an acid urine, then on the meeting of these different qualities of secretion a precipitate of free uric acid might be formed; and this might pass away as sand, or form concretions.

Hypothesis Concerning the Influence of Mechanical Arrestment of the Flow of Urine through the Ureters.—Uric acid is frequently deposited in the pelvis of the kidneys, even in cases where no organic disease of the kidneys seems to exist. This points to some participation of the infundibula and ureters in their processes. That urine may collect in the calyces of the kidneys we have every reason to believe. The contractile powers of the pelvis and infundibula become less with age; the lower part of

the pelvis may not be quite emptied of its contents, particularly in the erect position. I have even observed that in certain atrophic conditions of the kidneys, accompanied by the formation of uric acid gravel, the pelvis of the kidneys and sacs of the infundibula become so wide as to contain urine after death—a sure proof that they could not expel their contents during life, though there was no obstruction in the ureters. This condition only occurs in later life, to which renal concretions almost exclusively are proper. In children and young persons this affection is very rare.

OBSERVATION.—A man, *æt.* 65, died of cancer of the stomach. He had been a drunkard during the latter part of his life. I made the *post-mortem* examination of his body, and found a hard cancerous tumour involving the larger curvature of the stomach. There were also two large cancerous masses in the liver, whither the cancer had progressed by means of infesting the clot in the gastric veins, and in the portal vein. The cancerous juice most probably coagulated the blood; and the coagula became the beds of cancerous cell-development. Of this process all stages could be observed.

The kidneys were in a state of contractive atrophy, their upper halves more than the lower, which gave them a very peculiar shape. Their calyces contained several drachms of turbid urine. In the lowest part of the right calyx there lay a number of uric acid concretions, true red gravel. The ureters were quite pervious. The bladder contained no concretions of any kind. I could not ascertain whether the man had had any symptoms of gravel during life. If this was the case during the development of the cancer, the symptoms probably merged in the suffering attending this disease.

Crystallised Sediments.

The following observations serve to show the difference that may exist between cases in which a precipitate of uric acid formed in the bladder is one of the symptoms:—

OBSERVATION.—Mrs T—, *æt.* 75, had undergone great mental anxiety; and, in consequence, apparently lost her bodily health. There was loss of appetite, indigestion, and increase of the habitual constipation. There was headache over the eyebrows, with flushing of the face, and heat and dryness of the surface of the body. The urine, on being passed, was turbid, being mixed with a dark brown—almost black—sediment, appearing like fine coffee grounds. The sediment seemed to increase somewhat after cooling. Under the microscope it exhibited itself to be composed of rhombs of uric acid, mixed with a considerable amount of granular urates. A pill of a grain of powdered ipecacuanha, with four grains of rhubarb, taken before every meal, seemed to exert a very beneficial influence upon the digestive organs. An alkaline mixture, taken three hours after the principal meals, counteracted the heartburn. Under this treatment the deposit gradually disappeared.

June 12th, 1856.—After three weeks of apparently good health, another attack of gravel came on. The symptoms were—pain in the loins and chest and around the stomach, flatulency, want of appetite, prostration of strength, and headache. The bowels had been kept open by the rhubarb and ipecacuanha pills taken before meals; they even had been relaxed, a very unusual thing with this patient. The alkaline mixture soon restored her. The uric acid crystals were small, with double outline, dark brown, and were mixed with very light hexagonal plates.

28th.—There was a single discharge of gravel after some heat in the face,

pain in the stomach, and great flatulency. The deposit was most copious. The crystals were hour-glass shaped and ovoid. I did not prescribe any medicine on this occasion, but merely enjoined the patient to empty the bladder frequently.

A tonic plan of treatment was now adopted, which comprised quinine and iron as the pharmaceutical elements; cold sponging bath and exercise as the hygienic part; and rich diet, with a larger amount of spring water taken between meal-times, as the dietetic *régime*. The patient subsequently passed a small renal calculus and then remained free from any symptoms of renal concretions for several years up to her death, which took place from stenosis of the aortic aperture of the heart.

This case being one where the deposit was formed in the urinary organs, is a good illustration of a certain class of circumstances under which this may occur. The danger of the formation of a concretion is great in these cases. The best preventive measure is the free use of drink-water, and the frequent discharge of the urine from the bladder. In this manner the urinary passages are freed from dregs, and the urine is not allowed time to undergo decomposition.

The following case is very different from the former, as regards age and condition of the patient, and the symptoms under which the deposit occurred:—

OBSERVATION.—Master B—, a fine strong boy, nineteen months old, had suffered from severe bronchitis during the winter 1855–56, with congestion of the lungs, at one time bordering on pneumonia. He had a second severe attack in the early part of the spring of 1856, when at Boulogne. From both attacks he had perfectly recovered, when, at the beginning of May, his mother, then staying with him at Gravesend, noticed him to suffer from irritation of the bladder, the child being obliged to pass urine at least twelve or fifteen times in the course of the day. Immediately after the water had been passed, a red sand subsided to the bottom of the vessel. The child was well again next day, without any treatment having been had recourse to.

On June 14th, 1856, another attack of red sand came on, causing symptoms similar to those on the first occasion. The urine on passing contained a large amount of a light brown sediment of uric acid. The crystals were distinguished by their containing very little colouring matter, so that in strong light some almost escaped observation. They were all flat rhombic plates of different angles. The urine was highly concentrated; urea crystallizing spontaneously from a drop on a slip of glass.

In this case the disorder seemed to have some connection with the diet of the child, to which he either restricted himself or was restricted, namely, milk diet, taking for three meals nothing but milk, with bread and butter or biscuits. Whether the child got well spontaneously, as on the former occasion, or whether the change to a more mixed diet, with light vegetables and meat, had any share in the disappearance of the deposit, could not be decided. The deposit, however, did not reappear afterwards. This case seems worth noticing, as the uric acid deposit and the strangury caused thereby were the only disorders that could be discovered, the child being all the time as well and blooming as

one could wish any child to be. It is possible and probable that the strangury set up by the uric acid crystals in this and many similar cases of crystallised deposit, is the means of preventing the formation of concretions, and their retention in the urinary passages.

The urine of this boy, in which another sediment occurred after filtration, yielded some few crystals of uric acid on addition of acetic acid. But the case of the aged lady bore out the statement of Prout (*loc. cit.* p. 198), that the urine is so completely divested of lithic acid by a peculiar arrangement of the urinary principles, that on adding to it an excess of mineral acid, not another particle of lithic acid is usually deposited.

Another illustrative case of crystallised deposit formed in the urinary organs is recorded by G. Bird (*loc. cit.* p. 158, § 156).

In children who are liable to the formation of crystallised uric acid deposits in the bladder, symptoms of irritation about the urinary organs may, according to Prout (*loc. cit.* p. 202), be always more or less observed if the child be attended to. Thus there will be found frequent desire to pass urine, which is voided in very small quantities, and with manifest uneasiness. The irritation about the urinary organs also sometimes induces the child to wet the bed by night, &c. This irritation from the presence of crystallised deposits does not seem to exist in adult persons. It is not mentioned in Bird's case just quoted, and was not present in my first case.

Uric Acid Concretions.

1. *Sand and Gravel.*—*Crystalline Sediments.*—There seems at first sight to be no great reason for drawing any particular distinction between common uric acid deposits on the one hand, and sand and gravel on the other. Indeed, the common deposits of pulverulent uric acid are frequently called gravel and sand by medical men and by laymen. This practice, however, is not quite correct, and should therefore not be generally adopted. What we call "the common pulverulent deposit of uric acid" is made up of single crystals of that substance. The occurrence in such a deposit of twin crystals, crossed crystals, of crystals simply hanging together in a variety of ways, is an exception, and does not constitute a deposit of sand or gravel. To fall under the latter denomination, a deposit must exhibit a tendency towards a compound arrangement of the crystals—that is, the crystals must group themselves, with their predominant axis, round a common centre, like the rays round the luminous body from which they emanate. Mostly one or two large crystals form the basis of, or are mixed up with, these globular masses. What I should like to call "sand," therefore, would be masses of uric acid, mostly globular, or irregularly roundish, or oblong, of

very uniform size, from $\frac{1}{16}$ th to $\frac{1}{8}$ th of an inch in diameter, and answering to the above definition. Viewed by transmitted light under the microscope, the globules are perfectly impervious to light; and the uric acid crystals on the surface are faintly transparent, of a dark brown colour. To the naked eye the deposit is red, with a tinge of brown. When disturbed the sediment mixes with the clear urine, but rapidly subsides to the bottom when the fluid comes to rest. Generally, no small or well-defined crystals of the ordinary kind are mixed with this sand.

This description of sand is sometimes met with in the pale and watery urine of early infancy.

Under the name of "gravel," I would comprise concretions varying in size from $\frac{1}{16}$ th of an inch diameter upwards, until, by their size, they become incapable of passing either the ureters or the urethra. These concretions are generally rough; and if many are discharged at one time are of variable size, from that of a pin's head to that of an almond. A variety of these crystalline concretions are the "*pisiform*," "the formation of which is attended by a remarkable feature, namely, *the great number* in which they are usually generated, a circumstance which may be said to be characteristic of them. Their great number occasions them to accumulate occasionally in the pelvis of the kidney; or in the lower portion of the ureters, where they terminate in the cavity of the bladder; and on such occasions severe nephritic attacks are sometimes the consequence. These concretions vary in size, from that of a pin's head to that of a pea or marble. Their form is always more or less globular; though they sometimes present flattened or faceted surfaces, produced by their contact or attrition with each other. Their surface is usually smooth, sometimes even porcelainous or polished; and their internal texture is almost invariably crystallised, and usually lamellated. Their colour ranges through all the shades of yellow; and occasionally, though more rarely, they assume a dark brown or reddish colour" (Prout). These pisiform concretions are mostly deposited after the age of forty.

2. *Uric Acid Calculi*.—The number of calculi, of which uric acid forms either the nucleus or the entire substance is very great, standing to the number of all other calculi in the proportion of two to three. They are found of all sizes, from the largest pisiform concretions to stones of five or six ounces, or more, in weight. If formed in the pelvis of the kidney, a uric acid stone may have a very irregular rough shape and surface. If, however, the body and crust of the stone have been formed in the bladder, as is mostly the case, the shape will, in general, be that of a flattened ovoid, the flattening, in many cases, being so trifling as to escape notice. The exterior of the uric acid

calculus is slightly tuberculated; but in many cases the tubercles are so water-worn that the surface is smooth. In colour, uric acid calculi vary from reddish-yellow or fawn-colour to brownish-red, or brown with an admixture of red, like old mahogany. On being divided by a saw, they are seen to be composed of concentric layers, which are of variable thickness when compared with each other. But every layer preserves its own thickness pretty regularly all round the calculus. The texture of the stone is best seen on the surface of a fracture. In hard and pure stones it is crystalline, fibrous, the fibres of each layer verging like radii towards the centre of the stone. On breaking a stone, the fracture will mostly be parallel with these crystalline fibres. Stones, however, which are less dense and less pure are earthy, and amorphous in fracture. Some few stones are so hard that they give a ringing noise on percussion, a sharp sound like a pebble, and on being chipped exhibit a conchoid fracture. These stones are very dangerous, when they become the subjects of the process of lithotrity, for their fragments are so sharp that they wound the bladder, and cause infiltration of the urine into the adjacent cellular tissue; the consequences of which are mostly extensive mortification and death. It is, therefore, of high practical importance to ascertain the circumstances under which these hard stones may be formed.

The laminated structure of the uric acid calculi (and of all other laminated calculi) shows that they are formed by the gradual precipitation of uric acid from the urine, the precipitated substance being deposited in an equal layer all over the surface of the concretion, which forms the nucleus, and also over the surface of all subsequent layers; a circumstance which is the condition of the parallelism of the rings seen on section. The layers, however, show something more; namely, that the formation of the stone has been interrupted, or has taken place at different intervals. Of this circumstance there could not be given a better description than that of Prout:—"Between the different intervals at which the different laminae have been formed, periods have intervened during which no deposition has taken place. This remark not only applies to the different laminae of a heterogeneous calculus, but to the different laminae of calculi composed of the same substance; as, for instance, to the different laminae of which lithic acid concretions usually consist. This explanation is in perfect accordance with the circumstances attending the formation of calculi, which often, as is well known, remain in the bladder for a great number of years, without attaining any remarkable size. Moreover, the constant state of change alone to which the urine in all individuals is liable, almost precludes the notion of homogeneity in a calculus. We may suppose, therefore, that certain changes take place in

the urine, during which the law of continuity of deposition is suspended, and the surface of the concretion becomes, as it were, *water-worn* and less apt for future accretion; in short, assumes all the properties of a heterogeneous substance. Under these circumstances, when a tendency to deposition occurs, it will have to commence *de novo*, and, as it were, upon the surface of a foreign body. The consequence will be that the adhesion between the new and the old coats, or laminae, will be less firm than in the intermediate parts, and that a calculus thus formed will be disposed, when broken, to separate into concentric laminae." To this we have only to add that one great cause of the formation of layers is the periodicity with which the bladder is emptied of its contents. If uric acid is really precipitated by acid fermentation, and if for this fermentation to produce a sufficient amount of acid a certain time is required, during which the ferment must be in contact with the substance to be fermented, then no uric acid can be deposited immediately after the bladder has discharged its contents; and no uric acid can be deposited if the bladder is so irritable as to discharge its contents at frequent and short intervals, a condition which, as I have already stated, I believe to be the main safeguard against the more frequent occurrence of stone in the bladder. If, on the other hand, the calculus does not irritate the bladder at ordinary times, or is the mechanical cause of a retention of part or the whole of the urine, so that the urine has time to be collected and to be fermented, a deposition upon the calculus will take place.

Chemical Characters of Uric Acid Concretions.—The chemical characters are those of uric acid. But as the concretions may be more or less pure, it is advisable to follow a method in analysing. The blow-pipe decides whether the stone leaves any residue on combustion. A piece of the stone is then reduced to a powder, a weighed portion of which is extracted with ether, then with alcohol, and, at last, repeatedly with boiling water. The ether dissolves any fat; the alcohol takes up colouring matter; the boiling water removes urates and soluble inorganic salts, and a trace of the acid. If it is not necessary to be very accurate, the extraction with ether and alcohol may be omitted. The powder which is not soluble in water may now be dissolved in a dilute and warm solution of caustic potash or soda, and precipitated by carbonic acid, when white urate of soda will be mostly obtained. Or the solution in potash may be precipitated with acetic acid, when all the uric acid falls down in a very pure state, and is obtained by filtration, washing, and drying. The combined weights of the extracts and of the pure uric acid must be nearly equal to the weight of the powder taken for analysis.

Concretions consisting essentially of Urate of Ammonia.

These calculi, composed essentially of urate of ammonia, were discovered by Prout ("Med. Chir. Trans." x. 389). They are of rather rare occurrence, and seem confined to children under puberty. They are of small size, and have a smooth or slightly tuberculated surface, and a pale slate or clay colour, sometimes with an admixture of red or brown. In rare instances their colour is fawn, and in such stones pink layers occur towards the centre. They are composed of concentric layers, but the layers are much less distinct and much thinner than those of uric acid calculi. They have a fine earthy fracture, and are easily broken.

The *chemical diagnosis* rests upon the solubility of the urates in boiling water, by which they are distinguished from all other calculi. After the urates have been obtained in a pure state by dissolving and filtering, the uric acid may be precipitated by acetic acid, collected on a filter, washed, dried, and weighed. The filtered fluid contains the acetates of the bases with which uric acid was combined. We add hydrochloric acid, evaporate to dryness, heat with platinic chloride to precipitate ammonia and potash, wash with absolute alcohol and ether, evaporate filtrates, and expose the residue to a red heat, when soda and lime remain as chlorides. The residue is now dissolved in a little water, the lime is precipitated as oxalate by the addition of ammoniac oxalate, filtered, dried, and weighed. The filtered liquid contains the soda, which may be determined in the form of sulphate. In calculating the results, we apportion a molecule of base to every molecule of uric acid; any excess of acid was present in the uncombined state.

Layers of Uric Acid and Urates in alternating and mixed Calculi.

These layers are due to the same causes as the massive concretions. But there seems to be one cause of the occurrence of urates to which it is necessary to advert before concluding the chapter on uric acid. Ammonia at the temperature of the body very quickly changes uric acid into urate of ammonium. The urine in calculous disorders very frequently becomes alkaline; nay, if the disorder last long enough, ammoniacal decomposition of the urine in the bladder is almost always present. In evidence of this, almost one-half of all calculi possesses a cortical layer of mixed phosphates, the consequences exclusively of ammoniacal urine. Now there can be no doubt that if a uric acid stone become the cause of such disorders of the urinary passages as will induce alkaline fermentation in the urine, the outer layers of this stone must be transformed into urate of ammonia. A stone with a uric acid nucleus, a body of urates, and a cortical

portion of mixed phosphates, suggests the following history:—In the beginning there was a renal uric acid concretion, which increased in the bladder. Then the calculus caused disorder of the bladder, or of the urine (as by excessive treatment with alkaline remedies), which ended in the establishment of alkaline fermentation in the bladder, by which the outer layers of the uric acid concretion were first transformed into urate of ammonia, and afterwards encased in a crust of mixed phosphates.

Calculi composed mainly of urates frequently contain oxalate of lime and small quantities of phosphates in intimate mixture with the urates. They are then called *mixed calculi*.

NOTES TO URIC ACID.

Amorphous Sediment in Healthy Urine.

In England, on the authority of Prout, the granular sediment has been considered as urate of ammonia. Bence Jones ("Med. Chir. Transact." 27, 102, 1844) showed that it might be urate of ammonia changed in form by the presence of common salt.

That the amorphous sediment often differs in its reactions from any mixture of acid urates, was shown long ago by Berzelius and Lehmann.

In the 9th volume of the *Lehrbuch*, 1840, p. 418-419, Berzelius says, when speaking of the ordinary deposit:—"If, after the urine has become thick, it is filtered, and the sediment is washed on the filter and water is left to stand on it, often crystals may be found in a few hours."

In the 2d volume of his *Lehrbuch*, 1833, p. 355-6, Lehmann says, when speaking of the same sediment when filtered:—"If we examine the deposit on the filter directly, or after it has been treated with hot water to dissolve it, endeavour to make it pass through the filter, a quantity of the most beautiful uric acid crystals will be found, whilst in another portion of the same sediment which has not been filtered, not a trace of a crystal can be discovered." "In this experiment, although a large quantity of crystalline uric acid, free from soda, remained on the filter, yet the liquid which passed through the filter had not an alkaline reaction."

Lehmann attributes this liberation of uric acid to a change set up by the colouring matter, and Berzelius considered the crystals as urate of ammonia, formed by the action of the mucus of the urine. But the experiments of B. Jones have shown that the colouring matter and the mucus have nothing to do with the reaction.

Examination of Sediments of Urates.

Heintz (Müller's "Archiv." 1845, p. 230) filtered the urine before it became troubled, or redissolved the sediment by heat, filtered and allowed it to form again. He then collected or filtered, washed with water, and dried the residue on the filter.

A portion of this in a water-glass treated with caustic potash evolved ammonia, recognised by the white vapours which it formed upon a glass rod dipped in hydrochloric acid. 20 sediments all contained ammonia.

The other portion of the sediment was burned. 9 specimens yielded the following percentages of ash:—

4.26, 8.02, 3.20, 2.98, 5.63, 7.14, 6.20, 4.21, 3.61.

The actual amount of ash obtained varied between 0.002 and 0.006 gm. It was analysed as follows:—

The ash was extracted with little boiling water, the alkaline solution

filtered off and evaporated to dryness. The residue was dissolved in a little water and treated with hydrochloric acid, which caused the evolution of a little gas. The solution was then again evaporated to dryness and tested with the blowpipe. Soda was always recognised. The rest was used to separate potash by chloride of platinum. In two cases very small but indubitable quantities of potash were found.

The part of the ash which had not been dissolved in water was dissolved in hydrochloric acid under effervescence. The solution, made alkaline with ammonia, was treated with oxalic acid. In all cases a precipitate of oxalate of lime was obtained. The filtrate from this gave in one case only a feeble precipitate with phosphate of soda, showing the presence of a little magnesia.

The ash never contained hydrochloric, sulphuric, or phosphoric acid. Heintz prepared an artificial deposit by dissolving urate of ammonia in chloride of sodium. On cooling, a deposit ensued in amorphous granules which (formerly believed by Bence Jones to be urate of ammonia) was found to contain mainly urate of soda, only little ammonia, and an excess of uric acid, which, considering that the formula of uric acid was then half the present one, led Heintz to suppose that the compound was urate of soda combined with uric acid. The idea of the quadriurates, therefore, originally comes from Heintz.

The urates obtained by dissolving urate of ammonia in a hot solution of chloride of sodium and deposited after filtration, contain the more soda, the more concentrated the solution of chloride of sodium is. The deposits mostly contained uric acid, from 81.2 to 81.8 per cent.; oxyde of ammonium, from 0.09 to 1.41 per cent.; soda, from 12.64 to 14.92 per cent.; and urates (loss), from 2.96 to 4.14 per cent.

Another urate, *crystallised in needles*, was obtained by dissolving urate of ammonia in chloride of sodium, mixed with excess of ammonia. It contained uric acid, 88.35; NH_3O , 6.31; soda, 4.74; urates, 0.50 per cent. It losses all water at 100, while the above soda-salt retains one equivalent at 100.

The soda deposits can also be obtained by triturating chloride of sodium and uric acid together, and adding urates, afterwards ammonia, in the cold until its smell is clearly perceptible. The entire amount of uric acid is thereby transformed into an amorphous powder, or if more fluid is present, into larger balls, which contain uric acid, 81.34 per cent.; soda, 13.97; oxyde of ammonium, 0.35; acid urates, 4.43 per cent.

Heintz explains the formation of crystalline sediments of uric acid by the presence of a large amount of very acid phosphate. Against this speaks the circumstance that the uric acid does not redissolve on mixing.

The formation of the amorphous sediments of urates he explains by the reaction of various quantities of uric acid upon the phosphate of soda (in the presence of lime and ammonia salts). The three salts produced, namely, urates of soda, ammonia, and lime, precipitating together, cause the amorphous fine granular nature of the deposit. They always appear so when falling down in a solution containing chloride of sodium. The ammonia Heintz derives from the urea, the lime from the dissolved acid phosphate.

CHAPTER V.

XANTHINE, $C_5H_4N_4O_2$.

HISTORY AND LITERATURE.

THIS alkaloid, which in older publications is also termed *xanthic oxide*, and *uric oxide*, was discovered and first described by Dr. Alexander Marcet in his "Essay on the Chemical History and Medical Treatment of Calculous Disorders," 2d edit., London, 1819. It was subsequently observed by Laugier ("Journ. de Chim. Méd." 5 (1829) 513), constituting, as in the case of Marcet, a urinary calculus. A third calculus of this kind was discovered by the chemist Stromeyer, and by him presented to Wöhler and Liebig. The investigations of these authors ("Ann. Chem." 27 (1838) 340; Poggend. Ann. 41 (1838) 393) established the above formula, and many of the chemical properties of xanthine. It was believed to be a pathological product of the human economy, until Strahl and Lieberkühn, in their essay, "Harnsäure im Blut." Berlin, 1848, p. 119, showed that it was a normal ingredient of human urine. Ten years later, Thudichum ("Med. Times and Gazette," 1858, 2, 571) discovered the normal presence of xanthine in the human liver, both in health and disease. In the same year Strecker ("Ann. Chem." 108 (1858) 141) prepared xanthine artificially from guanine and hypoxanthine, and confirmed the constant presence of the alkaloid in human urine. Städeler ("Ann. Chem." 111, 28) enlarged these experiences, and Scherer ("Ann. Chem." 112, 257) extracted xanthine from the flesh of horses. He also explained that some of the reactions and properties formerly ascribed by him to hypoxanthine really belonged to xanthine, which had been obtained mixed with the other base. The chemical relations of xanthine, guanine, kreatine, &c., were discussed by Strecker ("Ann. Chem." 118 (1861) 116). Since then xanthine has been extracted also from the flesh of oxen and fishes, and may therefore be said to be a normal ingredient of muscular tissue; it is regularly found in the spleen, pancreas, and liver of the ox, and the thymus gland of the calf. It is also present in guano, and can be obtained from the mother-liquors of guanine by the acetate of copper process to be described below. In pathological conditions of the

human body, its quantity in certain organs, such as the enlarged liver or spleen, is increased; and it may be assumed that an increased production of xanthine precedes the formation, in the urinary bladder, of calculi composed of this substance.

Modes of obtaining Xanthine from Human Urine.—1. The following process is perhaps the most direct and convenient, as it dispenses with the difficulty of the evaporation of large quantities of primary material, which is a requisite in the processes to be described later on. The fresh filtered urine is made strongly acid with sulphuric and nitric acid, and treated with an acidified solution of phosphomolybdate of sodium, as long as a precipitate is produced. This is collected on a filter, and washed with water, acidified with sulphuric acid. It is then decomposed with baryta water in the water-bath, and the excess of baryta is removed by carbonic acid and boiling. The filtrate is treated with neutral plumbic acetate; then with basic acetate; and ultimately with basic acetate and ammonia; and the respective precipitates, containing all the xanthine and urochrome, are isolated. They are washed with water, united and decomposed with hydrothion. The hot yellow filtrate is evaporated and allowed to stand, when it deposits xanthine in crusts and granules; the urochrome, on the addition of alcohol, deposits more xanthine, and remains almost entirely in solution. The xanthine is dissolved in nitric acid, precipitated by argentic nitrate, dissolved in a little more nitric acid, with the aid of heat, and filtered from any argentic chloride which may be present. The solution is now treated with ammonia in slight excess, and the xanthine silver oxyde is collected on the filter and washed. It is next dissolved in boiling strong caustic ammonia, filtered, and the clear solution is boiled until the excess of ammonia is expelled, and the xanthine oxyde of silver compound is reprecipitated. After cooling, the precipitate is collected on a filter, and washed with water, ultimately dried at 150°. In that state it contains 56.2 per cent. of metallic silver. It is decomposed with hydrothion, and the sulphide is extracted with hot ammonia; this latter, on evaporation, leaves pure xanthine.

2. Strahl and Lieberkühn proceeded as follows:—More than fifty pounds of urine, from healthy persons of between 20 and 50 years of age, were evaporated to dryness. The residue was extracted with concentrated solution of caustic potash, which left earthy salts undissolved. The alkaline dark brown extract was treated with carbonic acid until no further precipitate was thereby produced. The precipitate was collected on a filter, and exhausted with water. Only a small residue remained on the filter, the alkaline solution of which, on the addition of hydrochloric acid, immediately deposited flakes of a reddish-brown substance. This was repeatedly dissolved in alkali, and repre-

precipitated by acid; an excess of acid retained it in solution. It had all the properties of xanthine. These authors also obtained xanthine from urine by treating it with caustic lime, and boiling it down during several hours. The filtrate, when exactly neutralised with hydrochloric acid, deposited a mixture of uric acid and xanthine, from which the latter was extracted with hydrochloric acid. This solution, on evaporation to dryness, left a greyish-white residue, which, after digestion with nitric acid, yielded a yellow reaction.

3. The urine is mixed with milk of lime until strongly alkaline, and filtered. The filtrate is evaporated to half its bulk, and while hot, is treated with a solution of acetate of copper, until a precipitate ceases to be produced. The precipitate becomes flaky, and assumes a light brown colour. The fluid, which has changed its alkaline reaction form an acid one, is now set aside, and after the precipitate has settled, is removed by the syphon. The precipitate is washed several times with water, and the latter is removed by the syphon; it is lastly collected on a filter, and washed with boiling water until the washings begin to get turbid; and if the precipitate is now analysed, it is found to contain xanthine, copper, lime, and uric acid. To separate these substances the precipitate is washed from the filter into a narrow-necked bottle, and suspended in a large amount of water. Hydrothion is now passed through it, until the fluid, after shaking in the stoppered bottle, smells strongly of the hydrothion. The sulphide of copper is allowed to deposit in a warm place, the supernatant liquid is removed by the syphon, the precipitate is thrown on a filter and washed with water containing hydrothion, and the filtrates are united with the decanted fluid. This solution in the cold quickly becomes turbid, and deposits needles and crystalline masses. It is cleared up by warming it on the sand-bath; and a solution of oxalic acid is added to it, until it ceases to produce a precipitate, and the fluid has assumed a strongly acid reaction. The mixture is now allowed to stand on the sand-bath for twenty-four hours, and stirred frequently. After that time all uric acid is deposited in crystals, mixed with the oxalate of lime. The deposit is separated by filtration, and the filtrate is freed from oxalic acid by treatment with carbonate of lime. When the boiling fluid shows an alkaline reaction, it may be filtered and evaporated to a small bulk. On cooling, xanthine is precipitated in the form of a light amorphous granular mass. The mother-liquor, which is very brown, is separated by filtration, and the precipitate on the filter washed with cold water until almost white, and until the washings are quite colourless. What remains on the filter is pure xanthine. The mother-liquor, by repeated evaporation, and standing, deposits the greater part of its xanthine, which may be

obtained pure like the first portion. The xanthine is now dissolved in a large quantity of hot water, and a dilute solution of nitrate of silver is added to it. A voluminous greyish-white precipitate thereby produced is a compound of xanthine and nitrate of silver. The fluid must be stirred and kept hot, while the last portions of the nitrate necessary for the complete precipitation of the xanthine are added, as the bulky gelatinous precipitate would otherwise inclose mechanically a considerable amount of uncombined nitrate, which it would be difficult to remove by washing. The precipitate becomes a little darker by boiling, but it is not blackened like the precipitate which nitrate of silver produces in acid urates. When the precipitate of xanthine and nitrate of silver is collected on a filter, it must be washed for a length of time, and then dried over sulphuric acid in the vacuum. When dried in the water-bath some silver is easily reduced, and the precipitate becomes black. During the process of drying, the large and bulky precipitate shrinks to a small compass. The bulky wet precipitate may be removed from the filter, and dissolved in concentrated fuming nitric acid. The assistance of heat quickens the solution, and lessens the amount of acid necessary. The dried precipitate may be dissolved in ordinary nitric acid, gently warmed. The solution, which is perfectly clear and somewhat yellow, on cooling and standing, deposits groups of needles of the xanthine and nitrate of silver compound. When they are left in the acid or other liquor for some time they resemble bundles of long hair emanating in curls from a centre towards all directions. This compound cannot be analysed very easily, as it loses silver and nitric acid during the process of washing. It has, therefore, to be decomposed, and the xanthine has to be obtained and analysed in the free state. This is best effected by treating the washed compound with ammonia, which removes nitric acid, and decomposing the remaining silver xanthine by hydrothion. The filtrate on evaporation yields xanthine mixed with sulphur, from which it is freed by solution in boiling concentrated caustic ammonia. In case the residue is yet coloured brown or dark yellow, its solution in boiling concentrated hydrochloric acid may be decolorised by animal charcoal. On repeated evaporation with ammonia, and extraction of the chloride of ammonium by water, pure, almost white xanthine is obtained.

The mother-liquor of these crystals contains yet much xanthine, which can be isolated as silver compound by the ammonia process above described, or the same as that which is applied to the crystals.

4. Strecker evaporated urine oversaturated with baryta water, and continued the evaporation of the filtrate until, on cooling, crystals of urea and chloride of sodium formed, which were removed. The filtrate was treated with acetate of copper, which,

on boiling, produced a dirty brown precipitate. This was collected on a filter, washed with boiling water, dissolved in warm nitric acid, and the solution, after addition of nitrate of silver, was allowed to cool and stand for some time. It deposited a compound which was collected on a filter, washed, and redissolved in boiling nitric acid, in order to free it from some chloride of silver. The filtrate, on cooling again, deposited crystals, which were freed from nitric acid by digestion with ammonia, diffused in water, and decomposed with sulphuretted hydrogen. The substance contained in the filtrate possessed the reaction of xanthine, and contained 5 carbon upon 4 nitrogen.

5. In my later examinations I have employed the following proceeding, which avoids the difficult operations with larger quantities of nitric acid:—Treat the urine, previously freed from uric by hydrochloric acid, with milk of lime, filter and precipitate with acetate of copper while boiling hot. Dissolve the washed deposit while wet in little nitric acid. Filter and add neutral acetate of mercury to the solution; separate and wash the yellow precipitate, and decompose it suspended in water with hydrothion. Evaporate the filtrate. To yellowish-brown dry residue add a little nitric acid and warm solution. Evaporate nitric acid on water-bath, dilute residue with water and filter, and add ammonia in excess to filtrate. White granular xanthine, with a yellowish tinge perhaps, will deposit on heating on the sand-bath, to be separated by filtration, washing, and drying.

Mode of Obtaining Xanthine from Calculi.—The calculus is dissolved in caustic potash, and the filtrate precipitated by a current of carbonic acid. The precipitate, which is white and pulverulent, is washed, and on drying, forms into hard yellowish pieces, which become wax-like on friction, and are free from potash.

Mode of Obtaining Xanthine from the Human Liver.—A fresh liver from a healthy or diseased person is minced and extracted with repeated quantities of boiling water. The extracts, after being united and filtered, are treated with a solution of acetate of lead, so long as a precipitate is thereby produced. A slight excess of the acetate is not hurtful. If the mixture does not clear up, and the deposit is slow in settling, it is well to keep it on a sand-bath over night at a moderate temperature (37° C). The filtrate is freed from lead by hydrothion, the sulphide of lead removing much colouring matter. The filtrate from this, a pale yellow-coloured fluid, is heated to ebullition to remove the hydrothion, and then evaporated to a thin syrup. This brown strongly acid extract, on standing for a fortnight, will generally be found to deposit on its surface a network of minute crystals, which, under the microscope, are of a triangular shape, with the three angles cut off by short secondary edges, in other words,

hexagons, with three long and three short sides. The crystals sometimes appear tetrahedral, but their small size makes it difficult to ascertain their shape, even with a quarter-inch object glass. The greater part of the deposit, in a pulverulent form, is found covering the bottom of the dish. The mother-liquor, after removal by means of a spatula of the surface crust, is decanted, the last portion with the deposit, however, being placed on a filter. Previous dilution with some water makes filtration easier. The deposit on the filter is washed with water until the water runs off pure.

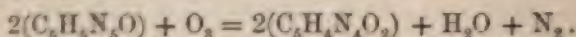
The substance now left on the filter is dissolved by caustic ammonia, cautiously added. The alkaline dark, but clear filtrate, is dried on the water-bath, when a lamellated yellowish substance remains. On spontaneous evaporation of this solution, some almost white thin crusts may be repeatedly removed from the surface of the solution. The residue is next dissolved in caustic potash, and precipitated from this solution by a current of carbonic acid gas. The precipitate, after filtering, washing, and drying, is a yellowish, reddish-white mass, which has the reactions of xanthine.

Mode of Extracting Xanthine from Horse Flesh.—The flesh is minced and placed in boiling water for a short time; it is then quickly withdrawn by a strainer; the broth is treated with baryta in the same manner as is directed for the preparation of kreatine, and is evaporated. Mixed with the crystals of kreatine is found a pulverulent deposit of xanthine. The mother-liquor is dissolved in water, and, while boiling hot, is treated with acetate of copper. The precipitate, treated with nitric acid and nitrate of silver, or with hydrothion, in the manner described for the precipitates from urine, yields much hypoxanthine, and little xanthine.

Transformation of Guanine into Xanthine.—Guanine is dissolved in boiling nitric acid of 1.15 to 1.20 spec. gravity. Small pieces of nitrite of potash are then successively thrown into the solution until a strong evolution of vapours occurs. The solution is then poured into cold water, and the lemon-yellow flakes which are thereby precipitated are washed, until the water which flows off does not any longer present an acid reaction. The substance is purified by solution in boiling water. From the first acid mother-liquor much yellow substance may yet be obtained by evaporation and partial neutralisation with carbonate of potash. This yellow product is a mixture of xanthine and a yellow nitro-compound much resembling xanthine, perhaps xanthine in which hydrogen is replaced by nitrous acid. Its exact formula has not yet been determined. It can be transformed into xanthine by the following process:—The yellow flakes are dissolved in boiling caustic ammonia. To the dark

red solution is added a solution of ferrous sulphate, until the precipitate of hydrated oxyde of iron which falls at first is superseded by a deposit of black suboxyde. The solution, which must yet contain much free ammonia, is filtered off, evaporated to dryness on the water-bath, and the sulphate of ammonia is extracted by water. The residue is again dissolved in boiling ammonia, and the solution again evaporated, when pure xanthine remains.

The metamorphosis of guanine into xanthine, leaving the intermediate products out of the question, is represented by the following formula :—



Transformation of Hypoxanthine into Xanthine.—When hypoxanthine is evaporated with nitric acid over the free fire, or treated with fuming nitric acid, a yellow residue remains on evaporation, which forms a reddish-yellow solution with caustic potash. On evaporation, it becomes violet-red at the margins, afterwards throughout of the same colour, and ultimately leaves a dark purple residue, which dissolves in water with a yellowish-red colour. This solution becomes colourless on addition of a solution of ferrous sulphate, and from the colourless filtrate acetic acid precipitates a body which has all the properties of xanthine.

Physical Properties.—Xanthine mostly appears in amorphous roundish granules, which, when dry, form a white or yellowish powder, and on friction with the nail assume the glistening appearance of wax.

Solubility in Water.—Xanthine obtained by evaporation of an ammoniacal solution, on boiling with water, dissolves to some extent. The saturated boiling solution contains 1 part of xanthine in 1310, 1380 (Strecker), 1178 (Städeler), 1148 to 1166 (Scherer) of water. But when xanthine is precipitated from its solution in alkalies, it at first yields one part to 396 parts of boiling water; on a second extraction, 1 part of xanthine is found dissolved in 570 parts of boiling water. This latter solution, on cooling, deposits flakes, and at 10° C. contains 1 part of xanthine in 2110 parts of water. Scherer in several experiments found 1 part of xanthine dissolved in 1650, 2901, 9488, and 2405 parts of water. Städeler in one experiment found 1 part of xanthine dissolved in 13,333 parts of water at 40° C.

From this it is clear that xanthine offers varying degrees of solubility, which may be caused by adhesion of foreign matters, condensation by heat, and other causes. It readily dissolves in alkalies, such as ammonia or potash, but does not dissolve so easily in hydrochloric, concentrated nitric, and sulphuric acids. When a solution of the substance in caustic potash is exposed to the air for some length of time, distinct

crystalline scales of the substance besides bicarbonate of potash are deposited.

The air-dry substance decreases little in weight at a temperature of 100, and after that undergoes no change by heating to 150°. When the heat is increased it blackens, and without fusing, gives, particularly when heated in an inclined glass tube open at both ends, a sublimate consisting partly of carbonate of ammonia, and partly of white unchanged xanthine, and evolves the odour of cyanogen and prussic acid. There always remains a carbonaceous residue. A watery solution of xanthine saturated in the cold gives a white precipitate with corrosive sublimate, but no precipitate with acetate of copper at the ordinary temperature; on boiling, however, a yellowish-green flaky precipitate is produced by this reagent. Nitrate of silver causes a gelatinous precipitate, which is little soluble or insoluble in dilute ammonia, but easily soluble in dilute nitric acid, with the assistance of a gentle heat; on cooling, the greater part of the xanthine compound is again deposited. The solution of xanthine in ammonia gives white precipitates with the ammoniacal solutions of the chlorides of cadmium and zinc, which are soluble in a great excess of ammonia. Acetate of lead produces white flakes, which, on standing, are frequently transformed into glistening crystalline scales.

Compounds.—Although the basic properties of xanthine are not so marked as those of guanine and hypoxanthine, yet it forms compounds which have much similarity with those of the latter bodies.

Sulphate ($C_5H_4N_4O_2 + SO_3H_2O + aq.$) is produced by dissolving moist xanthine in warm, not exactly concentrated, sulphuric acid, and crystallises in rhombic plates of the lustre of mother of pearl, which, by washing with water, lose their transparency, and leave pure xanthine in the original form of the crystals.

Nitrate.—On dissolving xanthine in moderately concentrated nitric acid, with the assistance of a gentle heat, no gas is evolved, and on cooling or evaporating the fluid yellow hemispherical or wart-like masses are deposited, which consist of very delicate crystals, and dissolve in potash without any very decided coloration. But when a nitric acid solution of xanthine is concentrated by boiling and dried, a lemon-yellow residue remains, which dissolves in potash with a yellowish-red colour, and on application of heat becomes violet-red. The lemon-yellow residue must not be overheated, as it easily and rapidly carbonises.

Hydrochlorate ($C_5H_4N_4O_2 + HCl$).—Xanthine dissolves easily in concentrated boiling hydrochloric acid; on cooling of the solution globules or wart-like masses are deposited, which consist of delicate, rhombohedral pointed scales, frequently interwoven, and of a silky lustre. When a concentrated solution is evapo-

rated on the water-bath, a crystalline pellicle is formed. The salt is soluble in 153 parts of the mother-liquor; it is little or slowly soluble in boiling water. It forms a double salt with platinic chloride, which has not yet been analysed.

Xanthine-Ammonia.—When xanthine is dissolved in concentrated warm ammonia, and allowed to stand in a stoppered bottle, a crystallised compound of the two bodies is obtained. From its solution in caustic potash the greater part of the xanthine is precipitated by acetic or carbonic acid in the form of flakes.

Xanthine-Baryta ($C_5H_4N_4O_2 + BaOH_2O$).—Boiling baryta water dissolves a little xanthine, and forms a compound.

Xanthine and Oxide of Silver ($C_5H_4N_4O_2 + Ag_2O$).—Nitrate of silver produces a precipitate in an ammoniacal solution of xanthine, which, after drying, has the foregoing composition.

Xanthine and Nitrate of Silver.—The addition of nitrate of silver to a solution of xanthine in dilute nitric acid produces a flaky precipitate, which dissolves on boiling, and reappears on cooling—the slower, the more free acid is present. In case the precipitates ensue quickly, they consist of membranous masses of hair-like confused crystals. By slower crystallisation radiary groups of fine needles are obtained. This compound, by washing with water, loses nitric acid and oxyde of silver,—more of the latter than of the former,—and therein differs from the analogous compound of hypoxanthine, which is not decomposed by water, much less soluble in boiling dilute nitric acid, and much quicker deposited from this solution.

Quantity of Xanthine Excreted in Twenty-Four Hours.—The urine of a patient suffering from disease of the kidneys with albuminous urine, granular casts, and uræmic symptoms, was examined on three successive days. The urine of twenty-four hours was freed from albumen by boiling, from uric acid by hydrochloric acid, from phosphates by excess of caustic lime. It was next boiled and treated with acetate of copper. The precipitate was dissolved in nitric acid, and the precipitate produced in this solution by acetate of mercury was decomposed by hydrothion, and the xanthine obtained purified, as described above. The following quantities were obtained:—

Quantity of Urine in Twenty-Four Hours.		Xanthine in same.
1st day, . . .	1500 c.c.	0.84 grains.
2d " . . .	2020 "	1.12 "
3d " . . .	1750 "	0.98 "

Neubauer obtained only one gramme of xanthine from about 600 pounds of urine, from which kreatinine had previously been precipitated. He probably separated only about one-tenth of the xanthine originally contained in this large amount of urine. He advises not to search for xanthine in less than one or two

hundredweights of urine. One day's healthy urine is, however, quite sufficient to obtain a quantity of xanthine which will suffice to give all its prominent reactions.

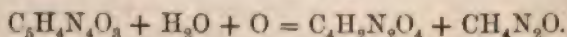
Xanthine Calculi.—Urinary calculi consisting of xanthine are light or dark yellowish-brown in colour, of even surface, hard in substance, of the hardness of the ordinary uric acid calculi, constructed of concentric layers without fibrous or crystalline texture. On friction, the calculi assume the glistening appearance of wax. The calculi examined by Marcet were given to him by Dr. Babington, who had obtained them from a patient of his. When, subsequent to the discovery of the peculiarity of these calculi, Dr. Marcet made inquiry of Dr. Babington, this physician had lost all recollection of the case and sight of the patient. Langenbeck in 1816 performed lithotomy upon a Hanoverian peasant boy, eight years old. The calculus was oval, but flattened, and of the size of a small hen's egg. It broke in three pieces on removal. The peculiar appearance caused Langenbeck to give the calculus to Stromeier, the then professor of chemistry, for chemical examination, who, from its chemical reactions, distinctly declared this calculus to be composed of Marcet's xanthic oxyde. Stromeier never published anything on this subject, but alluded to it in his lectures on animal chemistry. The history of the boy, as contained in the journal of the hospital at Gottingen of the year 1816, contains no data relative to the illness of the boy, during which the concretion was produced. The boy was dismissed cured four weeks after the operation; and, according to later inquiries, no symptoms of a renewed formation of calculus occurred to him.

It was upon the substance from this calculus that Liebig and Wöhler performed their analysis of uric oxyde. Pieces of the same calculus have latterly been analysed by Strecker, Scherer, and Städeler; and their reactions have been found by these chemists to accord with the reactions of the xanthine obtained by them from various parts of the human and animal economy, and artificially from guanine and hypoxanthine. A piece of this historical calculus is contained in the Museum of the Royal College of Surgeons, London.

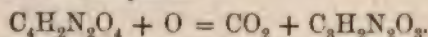
Laugier's Case.—Mr. L. had a disorder of the bladder, and had passed several small calculi. Some of them were given to M. Laugier by Dr. Laugier, under whose care the patient was. The largest calculus of three only weighed one centigramme (0.15 grains). The colour of the concretions was deep yellow, their form was spherical, and their surface seemed to indicate that they were uric acid. One of the calculi dissolved readily in caustic potash, without evolution of ammonia; but the addition of hydrochloric acid caused no precipitate in the fluid. An excess of ammonia produced no change in this solution. The

powder of the second calculus easily dissolved in concentrated nitric acid. The solution on evaporation left a citron-yellow residue, which dissolved in water with the same colour, and which, on repeated evaporation with nitric acid, always reappeared again. Potash, when added to the yellow mass, coloured it red on warming, and the intensity of the red colour increased by evaporation. This red colour, however, was transformed into yellow by solution in water. These reactions are in accordance with those described by Marcet.

Chemical Relations of Xanthine.—The composition of xanthine is so similar to that of uric acid that it was termed uric oxyde. It contains an atom of oxygen less than this acid, and, on the other hand, an atom of oxygen more than hypoxanthine. It is, therefore, by many considered as the middle term of a series of three bodies which stand in a genetic relation to each other, namely, hypoxanthine, $C_5H_4N_4O$; xanthine, $C_5H_4N_4O_2$; and uric acid, $C_5H_4N_4O_3$. That hypoxanthine satisfies the demands for proofs of this relationship, by admitting of its metamorphosis into xanthine, we have already seen. But xanthine has not yet been transformed into uric acid, nor into any of the proximate products of the decomposition of uric acid; and the direct relationship of uric acid to the series would thus be uncertain, but for the statement of Rheineck that uric acid could, by the reducing effect of a very dilute sodium amalgam, be metamorphosed into xanthine, and the latter, by the same agency, into hypoxanthine. But all the bodies of this group, including also guanine, as an amidated hypoxanthine, when treated with oxydising agents, yield a somewhat remote product of decomposition, which shows that they all have at least two radicals in common; and this product is parabanic acid, $C_2H_2N_2O_3$. This latter contains the radicals of oxalic acid and urea, into which it can be transformed in two stages; in the first stage it takes up a molecule of water, and becomes oxaluric acid, $C_3H_4N_2O_4$, and this again takes up a molecule of water, and then splits up into oxalic acid, $C_2H_2O_4$, and urea, CH_4N_2O . All the bodies yielding parabanic acid would therefore yield, by appropriate treatment, oxalic acid and urea, or their decomposition products, carbonic acid and ammonia. But in the case of uric acid, the formation of parabanic acid is known to be preceded by that of alloxan, urea being split off at the same time—

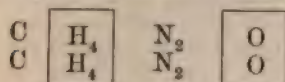


Alloxan is then transformed into parabanic acid by oxydation and loss of carbonic anhydride—

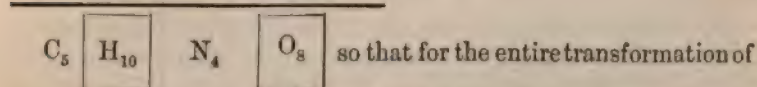
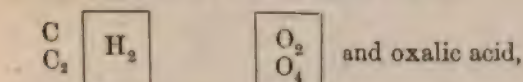


In the oxydation of xanthine and hypoxanthine, the form of

alloxan has not yet been observed; their radicals must therefore be arranged somewhat differently. In the case of uric acid, the nitrogen leaves in two stages as urea, and in that form only—



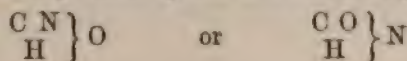
The carbon leaves as urea, carbonic acid



a molecule of uric acid into these final products, H_6 and O_6 are required, or $3\text{H}_2\text{O}$ and 2O . Xanthine would require one atom, hypoxanthine two atoms of oxygen more, to yield the same products as uric acid. From some reactions it is probable that xanthine contains the radicals cyanogen, glycolyl, carboxyl, and hydrogen; as an alkaloid, it may be a simple or a double ammonium compound. These possibilities have been expressed in two different constitutional formulæ—



These two formulæ stand in the same relation to each other as the two formulæ by which cyanic acid can be expressed—



NOTES TO XANTHINE.

Liebig and Wöhler determined the quantity of nitrogen by the proportion of its volume to that of the carbonic acid. 13 tubes containing 629.5 c.c. of mixture, lost 451.5 of carbonic acid when treated with caustic potash, and left 178 of nitrogen, giving the proportion of 1N to 2.53 of CO_2 , or 4N to 5C. Two errors in the original accounts of their analyses already corrected by Einbrodt ("Ann. Chem." 58, 15; and Unger, *ibid.* 58, 18), are clearly misprints, the quantity of uric oxide taken for combustion is stated to have been 0.2215 grm. instead of 0.4157 grm., as calculated from their results, and the proportion of gases in the mixture is 1N to 2.53 CO_2 , and not 1.5 CO_2 as stated. Unger repeated the analyses upon a part of the same calculus, and found the carbon to stand to nitrogen in the proportion of 5 to 4.

Literature.

of a solid of somewhat yellow colour. To this he believed that he had found xanthine, as it sometimes occurs, but he subsequently rectified his statement. He supposed the crude xanthine, after examination, turned out to be uric acid. The description of the reactions of this smaller calculus with nitric acid gives the impression as if they had beeniliary calculus from the composition consisting mainly of uric acid. Hebel also quotes Dulk in Schreivinger's Journal, 1840, as having asserted a xanthine calculus 7 grains in weight. But Dulk's name does not occur in that volume, which contains however in abstract of the essay of Marcet. The only other notice of xanthic oxide which occurs in Schreivinger's Journal is in 49, 188, where Marcet relates that he saw a calculus at Strömeyer's, in Göttingen, which this chemist analysed. Similar reactions performed in his presence, consisted of xanthic oxide.

To Mode of obtaining from Human Urine. (Strömeyer and Lieberkühn's.)

The foregoing summary I have extracted from a printed account, comprising twelve pages, 119 to 131. It is undoubtedly due to the want of precision in their descriptions that the researches of these authors were so long overlooked or misinterpreted. They also failed to repeat and confirm their experiments, so that to the recent accurate analyses they almost stand deprived of the credit of what was later in their discovery.

To Mode of obtaining from Human Urine.

This process was originally described on page 511 of the first edition of the treatise on the Pathology of the Urine, 1828, and the product stated to be uric acid, with which the silver compound and the reactions of the substance were much mistaken. The xanthine, as it is obtained pure by this process, without the help of nitric acid and silver, by dissolving the first granular deposit repeatedly in boiling caustic ammonia.

The nitrate of silver xanthine obtained in my investigation was repeatedly analysed until the constantly varying result led to the conclusion that the salt was decomposed by washing with water.

To Transformation of Guanine into Xanthine.

Strocker examined a portion of the xanthine calculus originally analysed by Liebig and Wöhler, and found its behaviour towards hydrochloric acid and that of its ammoniacal solution towards nitrate of silver to be the same as that of the product of the metamorphosis of guanine. Städeier, observing the different solubility of the two substances in water, was inclined to believe the xanthine from guanine to be a different acid, and proposed to term it guanine xanthine. But these notions have been set at rest by the observations on the varying solubility in water of all descriptions of xanthine. The xanthine from guanine is now allowed to be the same as that analysed by Marcet, Liebig, and Wöhler.

To Xanthine Calculi.

The calculus described by Dulk in Simon's "Beitrag zur Physiol. und Pathol. Chemie," p. 413, was not one of xanthic oxide as claimed by the author, but of uric acid. This is evident from the whole account, and particularly proved by the circumstance that on decomposition with nitric acid the calculus yielded crystallised alloxantine; a compound which has never been observed amongst the products of decomposition of xanthine, but only amongst those of uric acid.

CHAPTER VI.

HYPOXANTHINE, $C_5H_4N_4O$.

HISTORY AND LITERATURE.

UNDER this name Scherer ("Ann. Chem." 73 (1850), 328) described a substance which, though similar to xanthine in properties differed from it in elementary composition by containing less oxygen. He found it in the human spleen in individuals of all ages, and Gerhardt ("Würzb. Verhandl." 2, 299) found it in the blood of the ox. Scherer (*ibid.* 321) also discovered its presence in human blood in leukocythaemia, together with uric, lactic, and formic acids, and leucine. Although he correctly determined its elementary composition, the reactions described by him evidently belonged to a mixture of xanthine and hypoxanthine. Subsequently Strecker ("Ann. Chem." 102 (1857), 208, and "Chem. Soc. Journ." 10 (1858), 121, and again "Ann. Chem." 108 (1858), 129) described a base from the extract of flesh, which he named *sarkine*, and found to agree in composition with hypoxanthine, but to differ in reactions. Scherer ("Ann. Chem." 112 (1860), 257) thereupon proved the identity of sarkine and hypoxanthine, and explained the discrepancies between the reactions of his earlier hypoxanthine and that now admitted as pure, as having been caused by an admixture of xanthine. Hypoxanthine occurs normally in the brain of man and the ox in considerable quantity, and is probably not accompanied in this organ with either uric acid or xanthine. The liver, kidneys, thymus, and thyroid glands also contain a body much resembling hypoxanthine. It does not seem to occur in the human urine in health, but is excreted in pathological conditions, such as leukocythaemia, diseases of the liver, diseases of the kidneys, particularly albuminuria, with the large fatty kidney, and in obscure affections to be cited below.

Mode of Obtaining it Pure.—It is sometimes present in the muscular substance of the heart of the ox in such quantities that it is deposited from a boiling watery extract on concentration and cooling. From watery extracts of the brain it is also regularly deposited on concentration and cooling. But, as a rule, its solubility in extracts is so great that special precipitants are required for its isolation. Such are all specific precipitants of organic

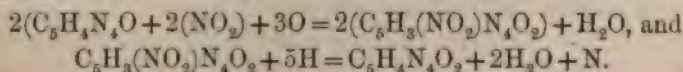
alkaloids, namely phosphomolybdic acid, mercuric chloride, tannic acid, and also argentic nitrate, mercuric nitrate, ammoniac zinc chloride, and cupric acetate. From brain extracts it is also conveniently separated by auric chloride.

The most advantageous method of preparing hypoxanthine from extract of flesh is by precipitation with cupric acetate. The diluted watery extract, for which the mother-liquor from kreatine preparation may conveniently be used, is heated to boiling and mixed with a dilute solution of the copper salt. The copious precipitate thus produced is decomposed by hydrothion, when the base remains in solution. To remove colouring matter the solution is boiled with hydrated lead oxide, which also takes up a small quantity of hypoxanthine. The filtrate from the lead is heated with hydrothion, and after filtration evaporated, when hypoxanthine is obtained in a crystalline form. That portion of hypoxanthine which remains in combination with the oxide of lead employed for purification may be recovered by decomposition of the residue with hydrothion, and extraction of the lead sulphide with ammonia. By carefully extracting with water one pound of raw beef, precipitating the extract with baryta water, evaporating the fluid, and precipitating it with a solution of silver nitrate in excess of ammonia, Strecker obtained one centigramme, indicating the presence of 2.22 parts of hypoxanthine in ten thousand parts of flesh.

From all kinds of animal extracts and fluids hypoxanthine can conveniently be removed by the following process:—The extract is strongly acidified with sulphuric and some nitric acid, and is then mixed with a solution of phosphomolybdate of soda, acidified with nitric acid, as long as a precipitate is thereby produced. The precipitate is washed with water containing some free sulphuric acid. It is then decomposed with a sufficiency of baryta water, added at first in slight excess, and, after digestion in the water-bath, neutralised by carbonic acid. The solution filtered hot, on boiling, deposits at first some baryum carbonate, but on concentration deposits the isolated alkaloids, amongst them hypoxanthine in scales, and, on standing, in hard crusts and masses. It is best to treat the entire solution with some nitric acid, and then with silver nitrate, to wash the precipitate slightly, and then to dissolve it in boiling dilute nitric acid, and filter on the steam-funnel. The solution almost immediately deposits the crystallised white compound of hypoxanthine and silver nitrate. All other alkaloids, whether precipitated by silver nitrate or not, remain in the nitric acid mother-liquors, and can be recovered by the phosphomolybdic process after removal of the silver by hydrochloric acid. Carnine, or acetylene-hypoxanthine, is insoluble in nitric acid, and, if present, would therefore remain with the silver chloride on the filter.

From the watery extracts of the human brain hypoxanthine is most conveniently precipitated by gold chloride. The precipitate is decomposed by hydrothion, and filtered hot. It is evaporated to a small bulk, and before the hypoxanthine hydrochlorate crystallises, is treated with caustic ammonia until alkaline, and again heated to drive off any excess of ammonia. On cooling and standing, hypoxanthine crystallises out. This is collected on a filter, redissolved in boiling water, treated with some animal charcoal, and again obtained white on cooling. To ensure its purity it is passed through the silver process above described. The silver is then removed by hydrothion, and the solution of the nitrate again treated with ammonia, when, after several recrystallisations, pure white hypoxanthine is obtained.

Physical and Chemical Characters.—From its warm saturated solution hypoxanthine, on cooling, is deposited in white flakes and crusts, consisting of masses of needle-like crystals; when a dilute solution of hypoxanthine is evaporated slowly, the substance adheres to the sides of the vessel as a dense crust; when evaporated quickly, desquamating scales are left behind. It is soluble in 300 parts of water of 15°; and in 78 parts of boiling water; it requires 900 parts of boiling alcohol for solution. The solutions do not change the colour of litmus paper, and exhibit no very characteristic taste. In hydrochloric acid, ammonia, and potash, hypoxanthine dissolves much more readily than in cold water; less readily in dilute nitric and sulphuric acid. It is very soluble in concentrated nitric and sulphuric acid, without discoloration or evolution of gas. Caustic alkalies, including baryta, dissolve hypoxanthine; from the solution in caustic potash or soda, the greater part of the hypoxanthine is precipitated by a current of carbonic acid gas; from the solutions in the fixed alkalies, and in ammonia and baryta, it is also precipitated by a little hydrochloric, or by an excess of acetic acid. Hypoxanthine is consequently an organic alkaloid of a very pronounced character. Of its chemical cleavage, nothing is known as yet, but its relations to xanthine are not only foreshadowed by its similarity to it in general properties, but established by its actual transformation into that body. Hypoxanthine is heated with fuming nitric acid, and the solution evaporated to dryness. The residue is mainly nitrate of nitroxanthine. Reduction by means of ferrous sulphate in ammonia solution removes the nitro-nucleus, and the solution yields xanthine—



The reaction is therefore similar to that by which guanine is transformed into xanthine. In the case of hypoxanthine,

hydrogen is substituted by nitrosyle; but in the case of guanine, amide is replaced by nitrosyle. Guanine, therefore, may be considered as amidated hypoxanthine. We have thus in the animal economy two products of the retrogressive metamorphosis of albuminous matters, of greater complication than hypoxanthine, both able to furnish this base, namely, guanine, $C_5H_5N_4O$, which would yield hypoxanthine by the loss of amide, and carnine, $C_5H_5N_4O_2$, which would yield hypoxanthine by the loss of acetic acid. The hypoxanthine would then take up oxygen, probably in *statu nascente*, and be secreted as xanthine in the urine.

Hypoxanthine presents great analogy to guanine in its compounds, in its behaviour towards nitrate of silver, sulphuric acid, baryta water, and caustic potash. But it can be distinguished from guanine by the following reactions:—The colourless nitric acid solution of guanine assumes a yellow colour on evaporation on the water-bath, and leaves a citrou-yellow residue, which, with potash, assumes a red colour, becoming violet on evaporation, purple on drying, and dissolving in water with a yellow colour. Hypoxanthine, on the other hand, dissolves in nitric acid of 1.20 spec. gr., without evolution of gas, and the solution by evaporation on the water-bath leaves a colourless mass, which dissolves in caustic potash without coloration, and does not become yellow unless very strongly heated; when the evaporation of the nitric acid solution is effected over the free fire, or fuming nitric acid is employed for the reaction, a yellow residue remains, which, on addition of potash, assumes a red colour. Xanthine has a very similar reaction. This alkaline red solution, on evaporation, becomes violet-red at the margins, and when dry, assumes the same colour throughout, ultimately becoming of a dark purple; it dissolves in water with a yellow colour.

The elementary composition of xanthine, $C_5H_4N_4O_3$, has suggested the idea that it might be a compound of uric acid and hypoxanthine—



but by mixing a solution of hydrochlorate of hypoxanthine with urate of soda, not xanthine but an isomeric compound, urate of hypoxanthine is obtained, which, under the influence of acids, separates into its original constituents.

Compounds.—The watery solution of hypoxanthine gives no reaction with most metallic salts at the ordinary temperature but a precipitate frequently ensues when caustic ammonia or potash is simultaneously added, or the fluid is heated to ebullition. Thus solutions of chloride or sulphate of zinc are indifferent, but

when an excess of ammonia is added, a white flaky precipitate of hypoxanthine-oxyde of zinc ensues, which is only little soluble in the boiling fluid. Chloride of cadmium shows a similar behaviour. Sulphate of copper gives a precipitate on the addition of potash, which is of a light blue colour, and remains unchanged by boiling. If the fluid contains an excess of potash, the precipitate blackens, and the hypoxanthine dissolves. A boiling solution of hypoxanthine gives a green flaky precipitate, with an excess of acetate of copper. Neither neutral nor basic acetate of lead, by themselves, precipitate hypoxanthine; but when it is boiled with the basic lead salt, a flaky white deposit is formed. On warming a solution of hypoxanthine with hydrated oxyde of lead, an alkaline solution of hypoxanthine oxyde of lead is formed, while a portion of hypoxanthine is retained in an insoluble state by the excess of hydrated oxyde. The following combinations with acids, metallic oxydes, and salts, are well defined:—

Hydrochlorate, $C_5H_4N_4O.HCl + H_2O$.—The solution of hypoxanthine in boiling concentrated hydrochloric acid deposits, on cooling, colourless crystalline plates, of the above composition. From a solution in dilute hydrochloric acid colourless crystalline needles are obtained on evaporation; when, however, the solution of hydrochlorate of hypoxanthine in water is repeatedly evaporated to dryness on the water-bath, a residue is at last obtained which contains no hydrochloric acid. Water has therefore a decomposing influence upon this salt.

Hydrochlorate of Hypoxanthine and Platinic Chloride, $2(C_5H_4N_4O.HCl)PtCl_4$. On adding a solution of platinic chloride to a concentrated warm solution of crystals of hypoxanthine hydrochlorate, the above platinum-salt is deposited in yellow crystalline masses, which are sparingly soluble in cold water, but readily dissolved at a higher temperature.

Nitrate.—The solution of hypoxanthine in concentrated nitric acid deposits, on standing, transparent, colourless crystals (apparently rhombic octahedra) of hypoxanthine nitrate, which on exposure to air or water become white and opaque, without any alteration of shape.

Sulphate.—The solution of hypoxanthine in concentrated sulphuric acid, deposits, on standing, or on addition of alcohol, colourless needle-shaped crystals of sulphate of hypoxanthine, which on coming in contact with water crumble to a white powder. The water dissolves some hypoxanthine and sulphuric acid, but the greater part of the base remains undissolved; the salt is consequently decomposed.

Hypoxanthine, when treated with concentrated acids at a temperature of $100^{\circ} C$. does not undergo any decomposition. Its solution, when mixed with aqua regia and evaporated on the

water-bath, leaves a residue which consists mainly of unchanged hypoxanthine.

Hypoxanthine and Baryta, $C_5H_2BaN_4O + 2H_2O$.—A solution of hypoxanthine in baryta water, on addition of a larger quantity of baryta water, deposits transparent colourless crystals of hypoxanthine baryta. From the solution of this salt the baryta may be precipitated by a current of carbonic acid gas.

Hypoxanthine and Silver, $C_5H_2Ag_2N_4O + H_2O$.—On adding a solution of hypoxanthine to an ammoniacal solution of nitrate or chloride of silver, a flocculent precipitate, quite insoluble in even boiling water and ammonia, but soluble in much concentrated ammonia, is obtained, which on drying becomes a hard mass like alumina.

Hypoxanthine and Nitrate of Silver, $C_5H_4N_4O + AgNO_3$.—A solution of hypoxanthine in water, when mixed with a solution of nitrate of silver, forms a flocculent precipitate, which is insoluble in dilute nitric acid at the ordinary temperature. It is, however, completely soluble in large quantities of boiling concentrated nitric acid, and from this solution is, on cooling, deposited in colourless needle-shaped crystals, and so completely, that the filtrate scarcely yields any precipitate on addition of hydrochloric acid.

Hypoxanthine in Human Urine as a Symptom of Disease.

In the following cases deposits of peculiar appearance were observed and interpreted, from the reactions of the bodies, to be xanthine. But the better knowledge of both xanthine and hypoxanthine which has been acquired since these observations were made, has rendered it probable that the deposits consisted of hypoxanthine. I point out this uncertainty, which in any future similar observations can easily be avoided by the adoption of the phosphomolybdate process and diagnostic silver-nitrate reactions.

CASE 1.—H. B. Jones, "Journal Chem. Soc." 15 (1862), 78. A boy, nine years and a half of age, had had good health until seven years old, when he was seized one night with violent sickness and pain in the stomach continuing for three days. On the third day his water gradually became of the colour of blood, it then stopped altogether and nothing was passed for four days; then delirium and convulsions came on, lasting for twenty-four hours, after which he was relieved by a most violent perspiration. No stone was seen to pass. In a few days he was perfectly well, and continued so for nearly three years, when in June 1861, he caught a slight cold and was delirious one night. A medical man saw him and found some albumen in the urine, which then was generally thick, and the quantity of deposit was increased by excitement or temper; cold produced the same effect in a less degree. He never complained of pain in the back, and was able to take much exercise without fatigue. He always had a good appetite, and was allowed to eat everything. On examination a very small quantity of albumen was found in the water made at night, and none in that made in the morning. There were no blood-corpuscles, no tubular casts, and the specific gravity was high. Many specimens were ex-

amined, but nothing remarkable was found. About the end of July 1861 the boy passed urine which was quite thick and deep coloured. A drop was placed under the microscope, and a crystalline deposit was found resembling one form of uric acid, but on the application of heat to the unfiltered urine the crystalline deposit entirely redissolved. Each fresh portion of sediment showed the same crystalline appearance and the same solubility by heat. A closer examination elicited simply that the crystals were not uric acid. A few days afterwards another specimen was observed containing the same crystalline deposit soluble by heat. The sediment formed about an eighth of the bulk of the fluid. It was collected on a filter, washed with alcohol and gave the following reactions:—It dissolved in water and in hydrochloric acid; when treated with nitric acid it dissolved without effervescence, and when evaporated to dryness it left a yellow residue. When the solution in hydrochloric acid was evaporated to dryness it left minute crystals, soluble in water. The sediment was easily dissolved by alkalies. The watery solution of the sediment had a feebly acid reaction, and when evaporated to dryness left an amorphous residue, which was again easily dissolved in water. The urine of this boy was examined on many subsequent occasions. It was generally of high specific gravity, 1025, 1026, 1027, 1030; once as low as 1013. It sometimes contained a trace of albumen, usually it deposited urates, and sometimes uric acid and oxalate of lime, but never the crystalline deposit soluble by heat and presenting the reactions of hypoxanthine.

CASE II. Observed by the author, and communicated to the Medical Society of London.—A gentleman, aged 49, who had been many years at sea, and undergone great hardships, had, during a period of indisposition extending over seven years, gradually become subject to confirmed disease of the liver and kidneys. When I examined him early in 1862, I found the left lobe of the liver enlarged, and projecting an inch and a half beyond its proper line towards the umbilicus. Its surface was uneven, and its substance hard, presenting the features of incipient cirrhosis. The bowels were mostly confined, requiring the assistance of purgatives. The evacuations indicated a very deficient action of the liver, by a peculiar light fawn or drab colour. There was great anasarca of the lower limbs, and some ascites. He had frequent pains in the region of the kidneys. The urine was collected and examined on four days, with the following result:—From January 29 to 30, during 24 hours, there were passed 860 c.c., or half the quantity which a person of the weight and size of the patient should normally pass. In colour it was brownish-red, and on standing in a warm place, deposited a large cloud of small epithelial hyaloid and granular, few fatty casts of the uriniferous tubules. Some of them contained amyloid bodies. When allowed to get cold, it became turbid, and deposited a large precipitate of urates, mixed with another matter, which, when the urates were decomposed by a little hydrochloric acid on the water-bath, at 37°, remained or reappeared in white prismatic crystals of microscopic minuteness. To the naked eye these crystals appeared as a white glistening powder, contrasting strongly with the dark brown large crystals of uric acid. When allowed to roll on the bottom of the glass vessel which contained them, they strongly reflected light, showing their crystalline nature. Under the microscope they appeared as small prisms, with pyramidal ends, and differed as much from the accompanying uric acid in appearance as their aggregate mass differed from it when inspected with the naked eye. They were separated by levigation, and then gave the following reactions:—They rapidly dissolved in caustic ammonia, and, after evaporation, their substance was deposited in granules, a small quantity only assuming the original shape of crystals. They dissolved in nitric acid without effervescence, and the solution on evaporation left a yellow stain. This became darker by gentle heating, and then dissolved in potash with a violet-red colour. The residue from the ammoniacal solution,

dissolved in hydrochloric acid, on evaporation, left prisms, with pyramidal ends of exactly the same form as the crystals originally obtained from the urine treated with hydrochloric acid.

The urine contained albumen, amounting dry to 163 grains in the whole urine of 24 hours. The urea weighed 400 grains. The uric acid was of average amount.

The urine from January 31 to February 1, 24 hours, amounted to 750 c.c., was brownish-red, yielded the same large deposit of casts of the uriniferous tubules, and a large deposit of urates and hypoxanthine. The dry albumen amounted to 164 grains, the urea to 359 grains; the uric acid was not weighed, as it could not be obtained pure.

From February 1 to 2 the patient passed 700 c.c. of urine, which was somewhat paler than the first specimens. It contained 133 grains of albumen, and 336 grains of urea. The uric acid was average, and not mixed with any deposit of hypoxanthine.

On the fourth day, February 2 to 3, the urine amounted to 750 c.c. The deposit of urates which occurred on cooling was much less coloured, and contained no hypoxanthine. The deposit of casts was still copious; the albumen amounted to 202, the urea to 359 grains. The patient suffered from an attack of diarrhoea. From this day he used the hot-air bath twice daily, and internally took gallic acid in large doses and cold extract of beef, with hydrochloric acid. This treatment diminished the dropsy to alight anasarca of the legs, the patient losing 22 pounds of weight in a fortnight, probably all by the abstraction of water; appetite and strength improved. The quantity of the urine rose to 1500 c.c. in 24 hours; it contained less albumen, more urea, was of a healthy colour, and made no deposits either of urates or hypoxanthine. It was examined on several subsequent occasions, and found to have maintained its improved character. By the continued use of the hot-air bath, which he had constructed at his own residence, the patient lost all symptoms of dropsy, though not the albumen and casts, from his urine. He lived for many years, and died from an acute attack of erysipelatous inflammation.

CHAPTER VII.

GUANINE, $C_5H_5N_5O$.

HISTORY AND LITERATURE.

UNGER, "Poggend. Ann." 65 (1844), 222; "Ann. Chem." 51 (1844), 395; 59 (1846) 58. Guanine discovered.—Gorup-Besanez and Fr. Will. "Ann. Chem." 69 (1849), 117. Guanine found in the excrements of spiders (epeira), in the "green organ" of the river crayfish, and in the "organ of Bojānus" of the freshwater mussel.—Strecker, "Ann. Chem." 118 (1861), 152. Transformation of guanine into xanthine, and decomposition products of guanine leading to urea discovered.—Barresswil, "Compt. rend." 53, 246. Guanine discovered in the scales of fishes.—C. Voit, "Zeitsch. f. wissenschaftl. Zoologie," 15, 515. Guanine in the swimming-bladder of a fish.—Scherer ("Ann. Chem." 112 (1860), 257 and 277) found guanine in the pancreas and liver of mammals. Guanine is here described mainly on account of its chemical relations to the uric acid group, and as the source of material for the study of the pathological relations of xanthine. For it is not certain whether guanine occurs in the human urine in health: the body sometimes believed to have been guanine is more probably xanthine. These substances might occur together, but the separation of small quantities of guanine from the xanthine would, no doubt, always be, analytically, very difficult. However, great care should be taken to attain this result; for, as hypoxanthine, which is not present in normal urine, has been found in abnormal urine,—particularly in connection with diseases of the liver and kidneys,—it is not improbable that guanine also may be excreted in analogous cases, as a product of impeded oxydation or premature excretion. The guanine which has been found in the animal organs above stated has been identified by chemical reactions only, and not yet by elementary analysis and atomic weight determination. As guanine is an ingredient of the shining silvery part of the scales of fishes and of their swimming-bladder, it is just possible that the guanine of guano—the excrements of seabirds living exclusively upon fish—may owe its origin to the skin and scales of the devoured fish, and may have

passed unchanged through the intestine of the birds, as guanine does when introduced into the stomach of a mammal. It may, however, also be a specific ingredient of the renal secretion of these birds. In the swimming-bladder of the fish *Sphyrna argentina* guanine is found in crystals resembling cholesterol, of which it is not known whether they are the pure base or a compound. The silvery matter of fish-scales seems to be a compound of guanine with lime, and is used for coating little glass bulbs inside, so as to give them the splendid appearance of real pearls.

The quantity of guanine met with in Peru guano is about a half per cent.; African guano contains less. Scherer obtained 0.0122 per cent. of guanine from the pancreas of the ox.

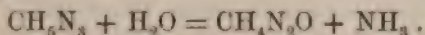
Mode of Obtaining it Pure.—Guano is boiled with water and milk of lime until a filtered sample of the mixture is not brown any longer, but has changed its colour to a pale greenish-yellow. During this process, which has for its object the fixing of colouring matter and the liberation of fixed and volatile alkalies, large quantities of ammonia are evolved, against the effects of which the operator, in case he works upon large quantities of material, should adopt special precautions. The boiling must be continued until all evolution of ammonia, on stirring the mixture, has ceased. This may last for more than twenty-four hours. It is now allowed to deposit the insoluble matters, and the supernatant fluid is filtered through a cloth. The residue in the copper is repeatedly extracted with small quantities of boiling water, and the filtrates are united. They are now neutralised with hydrochloric acid, and allowed to stand for some hours, after the lapse of which guanine and uric acid are completely deposited in the form of a reddish precipitate. This is washed, pressed in a cloth, and extracted with boiling hydrochloric acid, which dissolves guanine and little uric acid, leaving the bulk of uric acid undissolved. The acid solution, on cooling and standing, deposits crystals of guanine hydrochlorate, which are separated from the mother-liquor and purified by repeated recrystallisation. From the hot watery solution of this salt a slight excess of ammonia precipitates nearly pure guanine, in the form of a yellowish-white amorphous mass, which is washed and dried.

Strecker's Process.—Guano is boiled in water with some milk of lime. The solution is filtered off through a bag. This extraction is repeated until the filtrate is colourless. (These filtrates contain nitrate of urea, a body similar to xanthine, and other matters.) Guanine and uric acid remain almost completely undissolved. The residue is boiled repeatedly with sodium carbonate, until the filtrates cease to give a precipitate with hydrochloric acid. The united solutions are treated with sodic

acetate, and then with hydrochloric acid, until they present a strongly acid reaction, whereby guanine and uric acid are precipitated. The washed precipitate is treated with moderately dilute hydrochloric acid, and the solution separated from the uric acid by filtration. The hydrochlorate of guanine is decomposed by boiling with dilute ammonia, and the isolated guanine dissolved in strong boiling nitric acid; all uric acid is thereby destroyed, and, on cooling, yellowish crystals of pure nitrate of guanine are deposited. From their solution pure guanine, which is slightly coloured yellow, is precipitated by excess of caustic ammonia.

Physical and Chemical Properties.—Guanine has not yet been obtained in the crystalline state. It is a white powder, destitute of either taste or smell, or reaction upon vegetable pigments. It is insoluble in water, alcohol, and ether, little soluble in baryta or lime water, even on boiling, and precipitated from these solutions by carbonic or acetic acid; in the latter acid guanine is quite insoluble. It forms crystallisable compounds with strong acids; of these compounds the hydrochlorate is distinguished by producing double salts with mercuric, cadmic, zincic, and platinic chloride. Guanine may be subjected to a temperature of 200° C. without undergoing any change. When enclosed with water in a sealed tube, and heated to 250° C., it gives off a trace of ammonia, but otherwise remains undissolved and unchanged.

Decompositions.—On decomposition by chlorate of potash and hydrochloric acid, guanine yields the following products:—(a.) Parabanic acid (to be extracted from the evaporated residue by means of a mixture of ether and spirit); (b.) oxaluric acid (to be obtained by combination with baryta and precipitation with absolute alcohol); (c.) xanthine, obtained combined with baryta; (d.) guanidine, a base, which forms salts with acids, and on heating with excess of nitric acid forms urea according to the following equation—



Permanganate of potassium energetically oxydises guanine, producing carbonic and oxalic acids, urea, some ammonia, and an indifferent substance which is not crystallisable, has the composition $\text{C}_{10}\text{H}_{14}\text{N}_5\text{O}_9$, and has been termed oxyguanine.

When introduced into the human stomach, guanine, similar to uric acid, was found to increase the quantity of urea excreted in a given time; but when the dose thus introduced exceeded certain limits, a part of the guanine taken passed unchanged in the faeces (Kerner, "Ann. Chem." 103 (1857), 219).

Compounds—Nitroguanine.—A mixture of guanine and nitric acid, on evaporation to dryness on the water-bath, leaves a yellow residue, which is soluble in caustic alkalies with a deep orange

colour. This reaction consists in the formation of some oxalic acid, and of a compound of substitution, nitro-guanine, which, being itself a base, retains another molecule of nitric acid in combination ($C_5H_4(NO_2)N_5O.HNO_3$). In case the transformation into this new compound has been complete, its solution in caustic alkalies is not precipitated by either chloride of ammonium or carbonic acid; the latter, however, changes the orange colour of the solution back to yellow. If the two last-named agents produce a white precipitate in the alkaline solution of the nitric product, it is unchanged guanine. Nitroguanine can be transformed into xanthine by a process which has been described in the chapter relating to this latter substance.

Hydrate of Guanine.—Sulphate of guanine, when mixed with a large quantity of water, deposits the hydrate, which is separated from the dilute sulphuric acid, containing yet some guanine in solution, by means of the filter. The hydrate is very similar to anhydrous guanine, retains its water at $100^\circ C.$, but loses it at $125^\circ C.$, being 7.1 per cent. of its weight.

Hydrochlorate of Guanine. $C_5H_5N_5O.HCl + H_2O$.—This neutral hydrated salt crystallises from the solution of guanine in boiling strong hydrochloric acid on addition of a large quantity of hot water, and cooling in fine pale yellow needles; these give up their water of crystallisation in a continuous current of air, or at a temperature already below $100^\circ C.$, and thereby pass into the anhydrous modification, which, at a temperature of between 200° and $220^\circ C.$, gives up the entire amount of its acid, amounting to 19.27 per cent., leaving pure guanine. From the solution of the pure hydrochlorate, pure guanine is precipitated by sodic acetate. But from coloured hydrochlorate, sodic acetate precipitates a coloured guanine, and the reaction cannot be used for freeing guanine from colouring matter. For this object, precipitation of the hot solution by a slight excess of caustic ammonia is preferable.

The acid hydrochlorate contains two atoms of hydrochloric acid, viz., 48.14 per cent. It is obtained by saturating guanine with hydrochloric acid gas at a very low temperature, during a winter frost, or in a freezing mixture. The process is attended with intumescence of the guanine employed, and a slight evolution of caloric.

Nitrate of Guanine. $C_5H_5N_5O.HNO_3$.—Guanine is easily, and without decomposition, soluble in a boiling mixture of equal parts of nitric acid of 1.2 sp. gr. and water, and the solution, on cooling, yields a crystallised mass of hair-fine, concentrically-grouped, interwoven needles, which are best seen under the microscope. This is the mononitrated neutral salt; it has an acid, afterwards astringent taste, and a strongly acid reaction upon litmus paper; when exposed to the air it loses a little acid,

and effloresces; it is much more soluble in hot than in cold water, and is not changed by the boiling of the solution.

Guanine Baryum.—Guanine dissolves in boiling baryta water, and on cooling, colourless needle-like prisms are deposited, which over sulphuric acid become white, and contain 53.0 per cent of BaO. Theory requires 53.5 per cent. BaO.

Guanine Sodium.—Guanine is more soluble in caustic potash and soda than in acids. When a concentrated solution of soda is saturated with guanine, and mixed with a large quantity of spirit of wine, it deposits a lamellated mass of sodium guanine, which, after having been dried in the vacuum, loses yet 33.26 per cent. (12 molecules) of water at a temperature above 100° C. When exposed to the air the compound effloresces with absorption of carbonic acid, and liberation of guanine. It is not soluble in pure water, free from carbonic acid, without a partial precipitation of guanine.

Guanine Nitrate of Silver, $C_5H_5N_5O, AgNO_3$.—When a solution of nitrate of guanine is mixed with argentic nitrate, it deposits a copious precipitate. This is almost insoluble in even strong nitric acid in the cold, but dissolves on boiling, and on cooling is quickly and entirely deposited in fine colourless needles, which, after collection on a filter, washing with water, and drying, form a felt-like mass. They contain 33.6 per cent. of Ag.

Guanine Silver.—The foregoing salt, when treated with excess of ammonia, or any ammoniacal solution of guanine on being mixed with an ammoniacal solution of argentic nitrate, produces this compound.

Guanine Chloride Platinic Chloride, $2(C_5H_5N_5O, HCl) + PtCl_4 + 4H_2O$.—To a hot saturated solution of guanine in hydrochloric acid an excess of a hot concentrated solution of platinic chloride is added, the mixture is evaporated to half its bulk, at a temperature not exceeding 100°. The crystals which form on cooling are washed with spirit of wine and water, and dried over sulphuric acid. They are orange-yellow needles and prisms, yielding a citron-yellow powder. They become opaque over sulphuric acid, and lose a trace of hydrochloric acid. To a current of air of 15° they yield 6.51 per cent., or four molecules of water, together with a trace of hydrochloric acid, and leave a pale citron-yellow residue; this is with difficulty soluble in cold, but easily and entirely soluble in boiling water. The solution on cooling deposits the original crystals. The anhydrous residue does not yield any platinic chloride to absolute alcohol. Zinc and hydrochloric acid produce platinum black from the crystals, guanine remaining in solution. When the crystals are fused with sodic carbonate, sodic cyanide is formed. The crystals are easily soluble in caustic soda or potash, and in the car-

bonates of these alkalis without any evolution of carbonic acid gas, and from these solutions may be precipitated by acids.

Guanine Mercuric Chloride, $2(\text{C}_5\text{H}_5\text{N}_5\text{O}, \text{HgCl}_2) + 5\text{H}_2\text{O}$.—A concentrated solution of corrosive sublimate, when added to a concentrated solution of guanine hydrochlorate in such quantity that a sample of the mixture gives a yellow precipitate with soda, on stirring produces a crystalline precipitate of the above composition.

Guanine Cadmic Chloride.—Guanine also forms a compound with this salt.

Didagnosis of some Reactions of the Bases of the Xanthine Group.

Xanthine, purchased, dissolved in nitric acid and little water, gave a copious white precipitate with argentic nitrate, soluble in large excess of nitric acid on heating; this remained dissolved for some time after cooling, when a similar solution of *hypoxanthine* was already filled with crystals.

The *xanthine silver nitrate* compound was soluble in large excess of concentrated caustic ammonia, and gave a yellowish clear solution; a little coloured matter remained undissolved. This latter was surmised to be *nitroxanthine silver*, and together with the peculiar smell on first solution in nitric acid seemed to indicate that the commercial xanthine was probably made from guanine.

Xanthine made from guanine by myself behaved in every respect like the foregoing; it was, however, more yellow, and the part of the silver compound insoluble in concentrated ammonia was more coloured.

The *xanthine obtained from human urine* by the phosphomolybdic process described above behaved just like the foregoing; so also did the body separated from last urochrome by decomposition of this latter with acid, and reobtained by phosphomolybdic process; the products seemed, however, to contain different quantities of silver, indicating that the silver compound is not stable.

Guanine extracted by myself from guano behaved like the xanthines above described, but its silver nitrate salt crystallised a little easier than xanthine from dilute hot nitric acid; with a little more acid, however, it remained in solution like the xanthine salt.

These bodies therefore resemble each other—

- (1.) By their solubility in dilute warm nitric acid.
- (2.) Their precipitation from this solution by argentic nitrate.
- (3.) The solubility of this silver compound in much warm moderately dilute nitric acid.

But they differ by—

- (4.) Hypoxanthine silver nitrate being quickly deposited in crystals on cooling.
- (5.) Xanthine silver nitrate being deposited from a similar solution only after long standing.
- (6.) Guanine silver nitrate seems to be deposited at a period later than hypoxanthine, and earlier than xanthine.

They further resemble each other—

- (7.) By being precipitated as silver compounds free from nitric acid by a slight excess of ammonia added to the nitric acid solution just described.
- (8.) By the complete solubility of these silver compounds in a large excess of concentrated caustic ammonia.
- (9.) By the reappearance of the silver compound when the large excess of ammonia is allowed spontaneously to evaporate, or is expelled by heat.

CHAPTER VIII.

KREATININE, $C_4H_7N_3O$.

HISTORY AND LITERATURE.

IN 1835 Chevreul ("Journ. de Pharm." 21, 236), discovered a crystallisable substance in extract of beef of the Dutch Company, and termed it *Kreatine*. Nine years later Heintz ("Poggend. Ann." 62, 602; 70, 460; 73, 696; 94, 125) and Pettenkofer ("Ann. Chem." 52, 97) contemporaneously found a substance in human urine which gave a crystallised compound with zinc chloride, and which we now know to be a compound of kreatinine-zinc chloride with kreatine. In 1847 Liebig ("Ann. Chem." 42, 194, and "Chemical Research on Flesh and its Preparation for Food," Heidelberg, 1847, p. 47) obtained kreatine and kreatinine from the juices of the flesh of representatives of all the classes of vertebrate animals, and from the urine of men, and fully investigated their properties. Heintz ("Poggend. Ann." 74, 125) now showed that kreatinine was partly transformed into kreatine during the chemical processes required for its isolation, and that the parts and excretions of animals probably contained only kreatinine. Verdeil and Marcet ("Journ. de Pharm." (3), 20, 89) found kreatine in the blood of the ox. Dessaignes ("Ann. Chem." 97, 343) instituted researches into the chemical structure of kreatinine, in continuation of those first made by Liebig, and discovered the base methyluramine. Liebig ("Ann. Chem." 108, 354) next confirmed the observations of Heintz as to the transformation into kreatine of kreatinine contained in the urine of the dog. In the first edition of this treatise (p. 126) I published the first observations of the quantities of kreatinine and kreatine excreted in given times by healthy individuals. Neubauer afterwards ("Ann. Chem." 119, 127), published some further determinations of the quantities of kreatinine in human urine. Loebe ("Erdmann's Journ." 82, heft 3 and 4) investigated the solubility of kreatinine-zinc chloride, and Strecker ("Ann. Chem." 118, 165) published considerations on the chemical constitution of kreatine.

Occurrence.—Kreatinine and kreatine are both simultaneously obtained, by the processes to be related hereafter, from the flesh

of man the mammalia, of birds, amphibia, and fishes; from the urine of man and of many animals. But as these chemical processes give repeated opportunities for the transformation of kreatinine into kreatine, it is permissible to assume that both in flesh and urine kreatinine is normally present, and that it becomes partly transformed into kreatine during extraction. In the present state of our knowledge the existence of kreatine in flesh and urine is not proved.

Modes of Obtaining Kreatinine and Kreatine from Human Urine.

1. The most direct process is by the phosphomolybdic acid process already adverted to under xanthine, and which will be more fully described under the chapter relating to reducline and the alkaloids of human urine.

2. The urine is made alkaline with some milk of lime, filtered and evaporated until the salts are deposited. The mother-liquor is then separated from the salts (without the use of alcohol), and mixed with one twenty-fourth of its weight of a syrupy solution of neutral chloride of zinc. After the lapse of three or four days, a great part of the chloride of kreatinine zinc, with some kreatine, has crystallised in yellow, roundish, warty granules. The deposit is washed with water, then dissolved in boiling water, and to this solution hydrated oxyde of lead is added, until the fluid gives an alkaline reaction to test paper. The threefold amount of the oxyde of lead used up to this point is now added, and the fluid kept boiling, until it appears to coagulate into a light yellow magma. The decomposition is now completed. Zinc, hydrochloric acid, and lead in the form of the basic oxychloride are thus transformed into an insoluble condition; the kreatinine and kreatine combined with them before the addition of the lead remain in solution. The latter is now treated with some animal charcoal, which removes a yellow colouring matter and a trace of oxyde of lead, and is then evaporated to dryness. The crystalline residue, when heated with eight or ten times its weight of alcohol, either leaves a residue, or dissolves completely, and the solution deposits crystals on cooling; these crystals are identical in their properties with the residue, if any was left, and consist of kreatine. If these crystals are removed from the mother-liquor, and the latter is evaporated, a new crystallisation of a different form and different properties is obtained, which consists exclusively of kreatinine.

3. The urine is treated with excess of milk of lime, filtered, and the alkaline filtrate neutralised with acetic acid. It is then evaporated almost to dryness in the water-bath. The syrupy residue is mixed with strong or absolute alcohol, and allowed to stand for some hours. It is then filtered, and the other filtrate is mixed with a few drops of concentrated alcoholic solution of

neutral chloride of zinc, prepared by decomposing sulphate of zinc by chloride of calcium. The fluid is stirred energetically until it becomes turbid, and is then put into a cool place for forty-eight hours. The compound of chloride of zinc with kreatinine, which is almost insoluble in alcohol, is then found to be completely deposited. It is put on a filter, washed with alcohol, and is so pure that it may be dried and weighed. On decomposition in the usual way it always yields kreatine. This mode, originally devised by Heintz and Pettenkofer, was used by Neubauer in his quantitative determinations.

4. Dessaignes advises that the urine after treatment with lime should be reacidulated, evaporated, uric acid and salts filtered off, and the filtrate, neutralised with ammonia, should be treated with chloride of zinc. The proportion of zinc salt thus obtained, compared to the quantity of zinc salt obtained from urine evaporated in the alkaline state, is at the rate of 5 to 3.

Mode of Obtaining Kreatine from Putrid Urine.

If putrid urine, in which all urea is transformed into carbonate of ammonium, be boiled with milk of lime, until ammonia is not any longer evolved, the fluid then filtered, evaporated to a syrupy consistence, and treated with one twenty-fourth part of its weight of a syrupy solution of neutral chloride of zinc, there will, in the course of a few days, be deposited a considerable quantity of a yellow granular body, which contains chlorine and zinc, and, under the microscope, cannot be distinguished from the zinc salt obtained from fresh urine in the manner above described. When dissolved in boiling water, and freed from the chloride of zinc and colouring matter by means of hydrated oxyde of lead and animal charcoal, the organic substance, which was combined with the zinc, appears sometimes as pure kreatinine without any admixture of kreatine.

Mode of Obtaining Kreatinine from Kreatine.

If kreatine be treated with concentrated hydrochloric acid, the solution evaporated, and the dry mass heated in the water-bath until all free hydrochloric acid has been driven out, the residue consists of pure hydrochlorate of kreatinine. From this salt the kreatinine is obtained by boiling its solution in water with hydrated oxyde of lead.

In a similar manner kreatinine is obtained from the sulphate, by adding to the boiling watery solution carbonate of baryum, until the fluid shows an alkaline reaction, and no more carbonic acid is evolved. Sulphate of baryum is precipitated, and pure kreatinine remains in solution.

Separation of Kreatinine from Kreatine by Alcohol.

To effect this operation without loss for quantitative deter-

minations of both substances, I have employed the following apparatus:—A test-tube is mounted with a cork, perforated by two bent tubes after the manner of a washing-bottle. The lower end of the long tube dipping into the mixture to be extracted is closed by a little piece of calico, tied firmly over its slightly thickened end. The apparatus is fixed in a flask filled partly with water. If now the downwards bent tube is dipped into a small dish filled with absolute alcohol and suction is applied at the tube rising upwards, the alcohol will pass through the long tube and calico, and mix with the kreatine and kreatinine. On heating the water in the flask the alcohol in the test-tube will boil, and having done so for some time is forced by pressure through the long tube into a small flask ready for its reception. The calico retains all kreatine in the test-tube, and repeated extraction with new portions of alcohol will transfer all the kreatinine into the flask. The kreatine is dissolved in water, dried, and weighed. The kreatinine, after the evaporation of the alcohol, is also dried and weighed.

Physical Properties.

Kreatinine crystallises in the monoclinometric (clinorhombic) system. The crystals are formed by the prism ∞P , the basic terminal plane OP , and the clinodiagonal terminal plane $\infty P \infty$. The orthodiagonal is shorter than the clinodiagonal. The angle $OP : \infty P \infty$ (the angle, namely, at which the principal axis is inclined to the clinodiagonal) was found = $69^{\circ} 24'$. The angle at which the lateral planes ∞P coincide in the orthodiagonal section is = $98^{\circ} 20'$: and accordingly the angle formed by $\infty P \infty$ with ∞P is = $130^{\circ} 50'$.

Chemical Properties.

Kreatinine is much more soluble in cold water than kreatine. 1000 parts of water dissolve 87 parts of kreatinine, or one part dissolves in 11.5 parts of water at $15^{\circ} C$. In hot water it is much more soluble.

The watery solution restores the blue colour to reddened litmus paper. A crystal of kreatinine, placed upon a piece of wet turmeric paper, produces a brown stain on the spot where it lies. In concentrated solutions it has a caustic taste, like dilute liquor of ammonia.

Kreatinine dissolves in boiling alcohol, and crystallises from the solution on cooling. 1000 parts of alcohol at $15^{\circ} C$. dissolve 9.8 parts of kreatinine, 102 parts dissolve one part.

The chemical character of kreatinine is that of a strong alkali, exceeding in saturating affinity that of ammonia.

A moderately concentrated solution of nitrate of silver, to which a solution of kreatinine is added, coagulates immediately

into a mass of delicate white needles, which are easily soluble in hot water, but crystallise out of it on cooling, without having undergone any change. They consist of a basic combination of kreatinine with nitrate of silver.

In a solution of corrosive sublimate, kreatinine produces immediately a white curdy precipitate, which, in the course of a few minutes, transforms into a heap of delicate, transparent, colourless needles.

In a watery neutral solution of chloride of zinc, kreatinine produces immediately a crystalline precipitate, in the form of roundish, warty granules, which, under the microscope, are seen to consist of delicate needles in radiary arrangement.

Kreatinine expels ammonia from its salts, and forms blue crystallisable double salts with the salts of oxyde of copper.

Chloride of platinum produces no precipitate in solutions of hydrochlorate of kreatinine. If the mixture of the two solutions is, however, evaporated at a gentle heat, dark yellow, transparent, rather large crystals are formed, which are pretty easily soluble in water, less soluble in alcohol. This salt has a composition similar to the double-salt of chloride of platinum and ammonium.

Combinations.

Hydrochlorate of Kreatinine, $C_4H_7N_3O.HCl$.—On exposing crystallised kreatine in Liebig's drying apparatus, at a temperature of $100^\circ C.$, to a current of dry hydrochloric acid gas, the weight of the apparatus increases at first; on continuing, however, the high temperature and current of hydrochloric acid gas for some time, very nearly the original weight of the apparatus is at last obtained. During the experiment water is constantly seen to leave the apparatus, until the weight of the apparatus remains stationary. If dried kreatine be taken for the experiment, the apparatus shows an increase in weight. The body produced under these circumstances is neutral hydrochlorate of kreatinine.

In the same manner, hydrochlorate of kreatinine is obtained by dissolving kreatine in concentrated hydrochloric acid, in a porcelain dish, evaporating the solution, and heating the residue in the water-bath until all free hydrochloric acid has disappeared.

This salt contains one molecule of hydrochloric acid and one molecule of kreatinine. It is easily soluble in boiling alcohol, and crystallises from this solution in short, transparent, colourless prisms, which are easily soluble in water. On evaporation, it is obtained in large transparent laminae of an acid reaction.

It does not yield any precipitate with chloride of zinc, but when a solution of acetate of soda is added to the mixture of both salts, and the triple mixture is evaporated, kreatinine-chloride of zinc is easily obtained in a very pure state.

Hydrochlorate of Kreatinine and Chloride of Platinum.—A solution of hydrochlorate of kreatinine, when mixed with chloride of platinum and gently evaporated, yields rosy prisms of the double-salt. On rapid formation this salt is obtained in yellowish-red, transparent granules. It contains 30.95 per cent. of platinum.

Sulphate of Kreatinine.—On adding to one part of kreatine an equal weight of dilute sulphuric acid (composed of 27 parts of concentrated sulphuric acid and 73 parts of water), evaporating to dryness, and heating until all moisture is volatilised, neutral sulphate of kreatinine is obtained. It may also be produced by adding to a boiling saturated solution of kreatinine dilute sulphuric acid, until a strongly acid reaction is perceived, and evaporating to dryness. A white crystalline mass is thus obtained, easily soluble in hot alcohol. On cooling, the solution becomes milky, and, on becoming clear, deposits transparent, concentric, quadratic plates of neutral sulphate of kreatinine. They remain transparent and clear at a temperature of 100° C.

Chloride of Zinc and Kreatinine ($C_8H_{14}N_6O_2, ZnCl_2$).—On adding a syrupy solution of neutral chloride of zinc to a concentrated solution of kreatinine, a white granular precipitate is immediately produced. This may be filtered from the mother-liquid after twenty-four hours, and washed with cold water, in which it is very little soluble. It is much more soluble in boiling water, and crystallises from a saturated solution, on slow evaporation in large granules, warts, and groups of needles. It is very little soluble in concentrated spirit of wine and absolute alcohol. 1 part of the salt requires 9217 parts of alcohol of 98 per cent. strength, and 5743 parts of alcohol of 87 per cent. strength for solution.

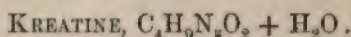
From its alcoholic solution kreatinine can therefore be precipitated almost entirely by the addition of chloride of zinc. This salt, mixed with kreatine, constitutes the substance originally obtained by Pettenkofer, and produced from urine by the first method.

From this salt and from the hydrochlorate, kreatinine may be separated by boiling with hydrated oxyde of lead, in the manner described for the first method. From the sulphate, kreatinine may be obtained by adding to its boiling watery solution carbonate of baryum, until effervescence is not any longer produced, and the fluid has got an alkaline reaction. Sulphate of baryum being thus formed, pure kreatinine remains in solution.

Transformation of Kreatinine into Kreatine.

Pure chloride of zinc kreatinine, prepared from kreatinine, decomposed as usual, yields a mixture of kreatine and kreatinine. Kreatinine in a flask with water, another with ammonia, in each

an excess of the base undissolved, after six months was found to a considerable extent transformed into kreatine. Sulphate of kreatinine mixed with milk of lime, and the solution filtered from the gypsum, yields a solution of kreatinine in lime water, which, after standing for eight months, on evaporation, yields a copious crop of kreatine crystals. The presence of neutral salts also favours this change, and still more so, but irregularly, the application of heat. Indeed, most operations in which kreatinine is set free, transform a part of it into kreatine. Long boiling with alkali, such as in urine treated with lime, according to Liebig's method, causes a transformation of kreatinine into kreatine, which may amount to two-fifths of the kreatinine actually present, and then partially escapes, partially enters the combination with zinc chloride.



Although kreatine, as such, has not as yet been found in the human urine by a process excluding the possibility of its formation from kreatinine during the operation, I here subjoin episodically an account of the modes in which it can be obtained from the juice of flesh, and a description of its physical and chemical properties and its decomposition products, as a guide to the student, who will certainly meet with this substance in every operation he may undertake for obtaining a specimen of kreatinine from human urine.

Liebig's Method of Obtaining Kreatine from Flesh.

In order to obtain kreatine pure, a quantity, say ten pounds, of flesh of a recently killed animal is freed of fat and finely minced; five pounds are then mixed with an equal amount of cold distilled water, carefully kneaded through by means of the hands, and then pressed strongly in a bag of coarse linen. The residue is now again intimately mixed with another five pounds of water, and again subjected to pressure. The fluid from the first pressing is put aside for further treatment to be described; the fluid from the second pressing serves towards the extraction of the second portion of the flesh. The first portion of flesh is a third time treated in a similar way with five pounds of water, and the fluid obtained by pressing is used for the second extraction of the second portion of flesh; the latter is treated a third time with pure water, and pressed.

The united fluids are filtered through a clean cloth, and filled into a large flask of glass; the latter is placed in a kettle with water, which is gradually heated to the boiling point, and kept at that temperature until the extract has lost its colour, and albumen and colouring matter have separated in the form of a

coagulum. If a portion of the fluid in a test-tube heated to boiling remains clear, this operation is completed.

The fluid is now separated from the coagula by filtration through a cloth, and subsequent pressing. The united fluids are then filtered through paper.

The colour of the fluid so obtained is reddish, if extracted from the flesh of the ox, doe, hare, or fox; but the fluid from the flesh of the calf, fowl, or fish is scarcely coloured. The extracts from the flesh of all animals are acid, from the presence of free acid, which must be removed before evaporating the fluid, as it would cause a dark brown colour of the concentrated fluid, and not permit the crystallisation of kreatine. In order to remove this acid, a concentrated solution of caustic baryta is added to the extract as long as a white precipitate is thereby produced. Neutrality or alkalinity should not deter the operator from adding the baryta solution as long as it produces any turbidity.

After separation from the precipitate, which contains all the phosphoric acid of the juice of flesh in the form of phosphate of baryum and magnesium, the fluid is evaporated in shallow porcelain dishes on the water or sand-bath, care being taken never to heat it to ebullition; the upper part of the dish must never get more hot than the fluid, as a ring of dry substance is formed thereby, which afterwards, on the addition of new portions of fluid, dissolves, and on further concentration imparts a brown colour to the fluid. The extracts from the flesh of fowl or fish remain colourless and clear to the last. If an excess of baryta have been added, a pellicle of carbonate of baryum is formed on the surface. The extract from the flesh of the ox, calf, or horse, at certain stages of its concentration, forms pellicles of organic matter on its surface, which must be removed as often as they are formed.

When the extract has been evaporated to about $\frac{1}{8}$ th part of its volume, and has assumed a syrupy consistence, it is put into a moderately warm place, and evaporation slowly allowed to go on; very soon there appear on its surface small, short, colourless needles of kreatine, which increase in number by standing and cooling of the fluid, so that the walls of the vessel gradually become covered by them. They are freed from the mother-liquor by filtration, washed with water, lastly with alcohol, and dissolved in boiling water. Should this solution be coloured, it is boiled with a little animal charcoal, and, after filtration, will be as clear as water. On cooling, it deposits kreatine in perfectly pure crystals.

According to Gregory, kreatine is obtained cheaply from cod, which, when chopped, well mixed with little more than its own weight of water, and pressed out, yields a fluid which, when neutralised (after the coagulation of albumen) by baryta, filtered to separate the phosphate of baryum, and gently evaporated till,

on cooling, it forms a thin jelly, deposits, on standing, kreatine in large crystals, nearly pure.

The heart of the ox is another convenient material, rich in kreatine, but the cheapest material from which to obtain it is urine.

Städeler's Method of Obtaining Kreatine from Flesh.

Flesh is minced, scraped, passed through a sausage machine, or triturated with rough glass powder in a mortar. It is then mixed with a little more than its volume of spirit of wine, the mixture is warmed gently on the water-bath, and the fluid is separated by pressing in a calico bag. The spirit is next distilled off; the residual fluid is treated with the necessary amount of solution of basic acetate of lead, the filtrate from the precipitate is treated with sulphuretted hydrogen, and the filtrate from the sulphide is evaporated to a syrupy consistence in the water-bath. After some days crystals are formed in the syrup, which are put upon bibulous paper to remove the mother-liquor, and on recrystallisation yield pure kreatine.

Physical Properties.

Kreatine crystallises in the clinorhombic system. The clinodiagonal inclined to the principal axis in an angle of $70^{\circ} 20'$; inclination of the planes $\infty P : \infty P$ in the orthodiagonal principal section = about $133^{\circ} 2'$. Specific gravity of the crystals = 1.35 to 1.34. The crystals are colourless, perfectly transparent, and lustrous. They are connected with each other in tufts and groups, and then resemble acetate of lead. They contain a molecule of water of crystallisation, which goes away at 100°C .

Chemical Properties.

Kreatine is easily soluble in boiling water; a solution saturated at that temperature becomes, on cooling, a mass of fine lustrous needles. From a dilute solution, however, kreatine crystallises very slowly in crystals, which may attain a length of from one-fourth to three-eighths of an inch, and a thickness of one-eighth of an inch, and will further increase in size if left in the mother-liquor for some time.

1000 parts of water at 18°C dissolve 13.44 kreatine, or one part of kreatine dissolves in 74.4 water.

In cold alcohol kreatine is almost insoluble, one part requiring 9410 parts of alcohol for solution. It is more soluble in spirit of wine containing some water.

The watery cold solution of kreatine, which contains a very small amount of that substance, has a weak bitterish taste and causes a sensation of irritation in the pharynx. If the solution

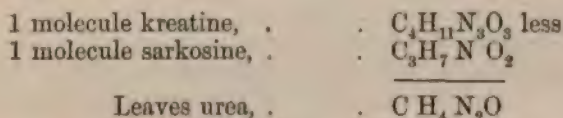
contains a trace of a foreign organic substance, it changes very easily, mouldy vegetations form in it, and it assumes a disgusting odour.

Kreatine, even in the largest quantity, does not neutralise the acid reaction of the weakest acids. Nitrous acid gas passed through a mixture of kreatine and water, dissolves the kreatine, and after some time nitrate of kreatine is deposited in crystals. Sulphate and hydrochlorate of kreatine can also be obtained by submitting mixed equivalents of acid and kreatine to evaporation below 30°C ., or in vacuo. It is soluble in baryta water at a higher temperature, but crystallises out of the cooling solution without having undergone any change. The crystals so obtained contain no baryta, and from the solution the whole of the baryta may be precipitated by carbonic acid.

Decompositions.

On being boiled with ten times its weight of crystallised hydrate of baryta in water, kreatine is decomposed, ammonia being evolved on the one hand, and carbonate of baryum in crystalline granules formed on the other. This decomposition will take place even though the air be entirely excluded from influencing the substance.

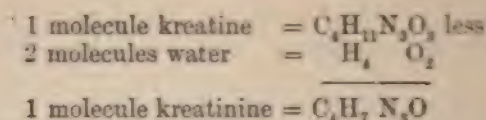
In solution there remains an organic base of the composition $\text{C}_3\text{H}_7\text{NO}_2$, sarkosine. This formula, when deducted from the elements of kreatine, leaves a formula which exactly corresponds to the composition of urea.



When the boiling is interrupted after the evolution of ammonia has began, the baryta is removed from the fluid by carbonic acid, and the filtrate is evaporated, it yields urea.

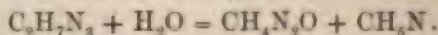
It is therefore evident that ammonia and carbonic acid are products of a secondary decomposition, and derived from the urea.

A solution of kreatine, to which at the ordinary temperature hydrochloric acid has been added, gives on spontaneous evaporation crystals consisting of unchanged kreatine. If, however, the solution is heated with strong hydrochloric acid, kreatine cannot be obtained any longer from the solution. The same effect is obtained by either sulphuric, phosphoric, or nitric acid. If kreatine is dissolved in one of these acids, and the solution is evaporated at a gentle heat, the kreatine is transformed into kreatinine, which crystallises in combination with the acid employed. This transformation consists essentially in the elimination from kreatine of two molecules of water



Kreatine, mixed with solution of chloride of zinc, and boiled for some time, causes the precipitation of a quantity of kreatinine—chloride of zinc. A warm, not boiling, solution of kreatine is not precipitated by chloride of zinc, and the crystals deposited from it are pure kreatine.

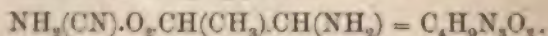
Kreatine and kreatinine, heated in watery solution with an excess of oxyde of mercury, are decomposed under evolution of carbonic acid; the fluid evolves a smell as if kreatine was subjected to dry distillation, and contains a new substance—oxalate of methyluramine. This salt is easily soluble in water, has a disagreeable taste, and becomes opaque on being heated to 100°C ., losing water. Treated with excess of milk of lime, filtered and evaporated in vacuo, methyluramine remains. It is a strong base, and forms salts with acids. Its composition is $\text{C}_2\text{H}_7\text{N}_3$. As kreatinine may be considered to be a compound of sarkosine and urea minus water, so the base may be considered as a compound of urea and methylamine minus water—



Methyluramine is the methyl-compound of a base obtained from guanine by chlorine, guanidine.

Kreatine can be considered as glycolate of methyluramine minus water, sarkosine as the amido-compound of glycolic acid, and methylamine. Methyluramine heated with potash evolves methylamine. This latter substance may be obtained from kreatine directly by heating with soda-lime.

Now, as kreatine by other modes of decomposition also yields methyl-parabanic acid, it can be considered also as a compound of cyan-amine and methyl-glycocol—



Sarkosine also yields methylamine by heating with soda-lime. Preferable, however, is the employment of peroxyde of lead and sulphuric acid. The sulphate is decomposed by chloride of baryum, and yields the chloride of methylamine.

Kreatine, oxydised by hot nitric acid, also yields methylamine. Kreatine oxydised with peroxyde of lead and sulphuric acid yields sulphate of methyluramine.

Kreatinine in water, treated with nitrous acid gas, effervesces, and forms the nitrate of a very feeble and, by itself, insoluble base of the composition $\text{C}_4\text{H}_{10}\text{N}_6\text{O}_3$, which, heated with excess of hydrochloric acid to 100°C ., forms oxalic acid, chloride of ammonium, and the substance which Liebig found to accompany

sarkosine, probably $C_4H_4N_2O_3$. A small quantity of this base is obtained as a white powder, when nitrous acid gas acts upon kreatine.

Physiology of Kreatine.

Kreatine being present in the muscles, striated and organic, of all classes of vertebrate animals, and being absent from the brain, liver, and kidneys of the same animals, it becomes highly probable that it stands in a certain relation to the chemical changes in these organs in which it is found. It seems to be a product of the chemical action induced in the muscle by the influence of motion. For in wild and hunted animals, such as foxes and game, the quantity of kreatine contained in the muscles is much larger than in domesticated animals. This difference in the amount of kreatine produced in the muscular tissue is very strikingly exhibited in the same class of animals.

A fox which had been fed on meat for two hundred days at the Anatomical Institution in Giessen, did not yield one-tenth part of the quantity of kreatine which was obtained from an equal weight of the flesh of wild foxes which had been shot.

The amount of kreatine contained in the muscles of an animal stands in a close relation to the quantity of fat deposited in the animal, or to the causes which determine the deposition of fat. From fat meat there are frequently obtained only traces of kreatine, and under all circumstances a much smaller quantity than from lean meat with an equal amount of fibrous matter. The above-mentioned fox, which had been fed on meat, yielded above one pound of fat from the peritoneal folds, while in wild foxes no fat was perceptible to the eye. The heart of the ox, a never-resting muscle, contains 1.3 per mille of kreatine, and is therefore frequently used for producing it in quantities.

The flesh of fowls contains 3.2 per mille, that of codfish 0.9 to 1.7 per mille. The quantity of kreatine obtained from the flesh of man is 0.67 per mille, or about the same quantity as from beef.

Kreatine is truly excrementitious; its relation to urea proves this beyond doubt. Its exclusive occurrence in the muscles shows the seat of its formation; it is, with other matters, a product of the chemical changes in the muscles.

Quantity Discharged in Twenty-Four Hours.

This question seems of sufficient importance; but few observations have been made on it. My own experiments, detailed at the end of this chapter, yield 0.305 grammes of kreatine discharged in the urine during twenty-four hours, as the average of twenty-six days of two individuals.

The average of kreatinine obtained from the urine of the same individuals at the same time was 0.44 grammes in 24 hours.

Calculating both quantities, without regard to the slight difference in composition as kreatinine, as which they were undoubtedly present at the time of excretion from the body, we have 0.745 grammes of kreatinine as the average amount excreted by each of these two individuals in 24 hours.

Neubauer found that a healthy man taking mixed food excreted from 0.6 to 1.3 grammes of kreatinine in 24 hours dissolved on an average in from 1500 to 1600 c.c. of urine. Several other adult persons excreted from 0.8 to 0.9 grammes per day, and a boy yielded 0.4 grammes in 24 hours.

Variations of Kreatinine Dependent upon Variations of Food.

We possess a very striking illustration of this relation in an observation made upon a dog by Liebig. This animal had, in the course of Bischoff's observations, been fed upon meat only, then upon meat and fat, and lastly upon fat only. It had voided various quantities of urine, which, for the sake of preservation and the removal of phosphoric acid, had been mixed with milk of lime. On evaporation, the urine taken during flesh diet gave a crystallisation of urea; when this was extracted with alcohol, a white powder remained undissolved, and was found to be about 60 grammes of pure kreatine. This urine contained only traces of kynuric acid. When, however, only little or no meat was given, and the dog lived upon fat mainly, considerable quantities of kynuric acid were obtained by hydrochloric acid and rest, and kreatinine seemed to recede.

Variations of Kreatinine in Disease.

In disease the quantity of kreatine, together with that of kreatinine, might serve to indicate the intensity of any spasmodic or convulsive action. The question as to its quantity in tetanic and epileptic disease is one of high interest. Cases of paralysis agitans, in which the spasmodic action ceases with sleep, may perhaps afford good opportunities for demonstrating the influence of rest and motion; though the different nutrition in the muscle may perhaps vary the chemical changes in some degree.

On the alleged researches of Schottin ("Archiv. für Heilkunde," 1860, 417), see note in appendix.

Observations on the Quantity of Kreatinine and Kreatine Discharged in given times by Healthy Individuals.

Observation 1.—Five days' urine from A, 28 years of age, weight of body 70 kilogrammes, was treated for kreatinine and kreatine by Liebig's process. The zinc salt was decomposed by hydrated oxyde of lead. The mixture of the two substances obtained was separated by alcohol; the alcoholic solution of krea-

tinine was evaporated to dryness in a water-bath. The drying process was completed with a chloride of calcium tube and an air-pump. There was obtained kreatinine, 3.1292 gm.

The kreatine which constituted the residue from the alcoholic extraction was washed into a silver capsule with boiling water, and evaporated to dryness. Its weight was 2.0475 gm.

This gives 0.6258 gm. of kreatinine per day, and 0.4095 gm. of kreatine per day.

Observation 2.—Four days' urine from *A*, treated as usual, the zinc salt decomposed with lead, no charcoal used.

There were obtained kreatinine, 1.4532 gm., equal to 0.3633 gm. for twenty-four hours.

The alcoholic extraction left kreatine, 1.2120 gm., equal to 0.3030 gm. for twenty-four hours.

Observation 3.—Two days' urine from *B*, aged 28, weight of body 72 kilogrammes. There were obtained two portions of chloride of zinc kreatinine, the second portion not quite pure. It was therefore recrystallised, and, together with the first, dissolved in boiling water. The zinc was then precipitated by sulphuretted hydrogen, after a little ammonia had been added to the solution. The mixture stood for several days to allow of perfect precipitation of the sulphuret of zinc. But when the filtrate was evaporated, redissolved, and, after a new filtration, re-evaporated, there was always again sufficient sulphuret of zinc formed to constitute an impurity. During these proceedings it was found that the ammonia which had been added, and which must have formed chloride of ammonium with the hydrochloric acid from the zinc salt, was gradually driven out by the kreatinine, and the last portions of it disappeared with the alcohol which evaporated from the kreatinine. The hydrochloric acid was removed with oxyde of lead and charcoal, the filtrate evaporated, the mixture of the residue obtained was separated by alcohol, and the quantities of substances obtained were as follows:—

2 days' kreatinine,	0.8182 gm.
2 days' kreatine,	0.6185 „

The kreatine contained yet a very slight amount of kreatinine; the figures for kreatinine are therefore somewhat below the actual amount, those of kreatine a little higher:—

1 day's kreatinine,	0.4091 gm.
1 day's kreatine,	0.3092 „

Observation 4.—Five days' urine from *B*, yielded 4.363 gm. of chloride of zinc kreatinine (and kreatine as an admixture.) After having been dissolved in boiling water, and made alkaline

with ammonia, a current of sulphuretted hydrogen was passed through the solution for several days; the yellowish-white sulphuret of zinc was thereby precipitated. The filtrate was boiled for a length of time to drive the ammonia out of its combination; it was then evaporated, and the dried residue was treated with alcohol. There were obtained, chloride of kreatinine, 2.4072 gm., which is equal to 2.93 gm. chloride of zinc kreatinine, which, deducted from the above 4.363 gm. of zinc salt, leaves 1.433 gm. for the kreatine contained in the zinc salt as an admixture.

The kreatine obtained weighed 1.1201 gm.

Kreatine calculated, .	1.433 gm.
Kreatine found, .	1.1201 "
Loss, .	0.3129 "

This loss, when distributed over the different operations, and in part accounted for by the abstraction of colouring matter by the lead and the charcoal used for the purpose, is intelligible. The experiment illustrates the proportions between the kreatine on the one hand, and the kreatinine zinc salt on the other, contained in the crystallised substance obtained from the urine.

Secreted in 5 days, kreatinine,	1.8322 gm.
" " kreatine,	1.1201 "
Secreted in 1 day, kreatinine,	0.3664 "
" " kreatine,	0.2240 "

Observation 5.—Five days' urine from *B*, yielded 6.7663 gm. of crystallised substance (chloride of zinc kreatinine and kreatine mixed), washed and dried. From this the amount of kreatinine and kreatine was ascertained by calculation, upon the basis of the parts found in the fourth observation.

4.3630 gm. of crystallised zinc salt yielded 1.8322 gm. of kreatinine; therefore 6.7663 gm. of zinc salt prove 2.8373 gm. of kreatinine, and 1.7370 gm. of kreatine to have been secreted during five days.

Excreted in 1 day, kreatinine,	0.5674 gm.
" " kreatine,	0.3474 "

Observation 6.—Five days' urine from *A*, yielded a quantity of crystallised zinc salt, which was washed, redissolved in boiling water, filtered, evaporated, and dried. When dry, it was a powder-like mass of a light yellow colour, a sample of which, when burned on platinum foil, left pure oxyde of zinc on the foil. When exposed to the air, it attracted very little moisture. Its weight, when properly dry, was 4.6324 gm. The amount of kreatinine and kreatine was calculated upon the basis of observa-

tion 4—1.9453 grm. of kreatinine contained in the zinc salt; 1.1892 grm. of kreatine contained as an admixture in the zinc salt.

There was a second portion of crystallised substance obtained from the mother-liquor. It was, however, impossible to free it from impurities, and it could, therefore, not be approached by quantitative analysis. The above values are, therefore, only expressive of a minimum, since there was certainly more kreatine and kreatinine present in the urine than could be obtained pure.

The above observations of the quantity of kreatinine and kreatine discharged by healthy individuals in a given time, have been arranged in the following tables:—

Individual.	Number of Observations.	Number of days observed.	Grammes of					
			Zinc salt obtained from urine.	Kreatinine of relative days.	Kreatine of relative days.	Average of kreatinine in 24 hours.	Average of kreatine in 24 hours.	Calculated average of kreatinine.
A, man, 28 years of age, weighs 70 kilogrammes.	1	5	...	3.1292	2.0475	0.6258	0.4095	
	2	4	...	1.4532	1.2120	0.3633	0.3030	
	6	5	4.6324	1.9453	1.1892	0.3890	0.2378	0.745
B, man, 28 years of age, weighs 72 kilogrammes.	3	2	...	0.8182	0.6185	0.4091	0.3092	
	4	5	4.3630	1.8322	1.1201	0.3664	0.2240	
	5	5	6.7663	2.8373	1.7370	0.5674	0.3474	

NOTES TO KREATININE, &c.

To Städeler's Mode of Obtaining Kreatine.

I have on one occasion treated 18 pounds of fresh dogs' flesh with methylated alcohol. The operation of extraction was very agreeable, but the distillation of the extract was very difficult. The ultimate extract yielded me much less kreatine than a similar amount of water extract would have done. But a little more kreatinine chloride of zinc was obtained, when after removal of the kreatine, this salt was added. After long standing, lactate of zinc and xanthine zinc were found deposited.

To Variations of Kreatinine in Disease.

Parkes ("The Composition of the Urine," p. 21) gives an abstract of the paper by Schottin alluded to, which concludes with the remarks:—"The

objection to these observations is, that we are hardly yet acquainted with the physiological excretion of kreatine. Either Schottin has placed it too low, or Thudichum too high."

Any person acquainted with chemical analysis can see at a glance that, of the proceeding adopted by Schottin for extracting kreatine and kreatinine from urine, failure is more likely to be the result than success. I had formed my own opinion of the paper of Schottin,—“the result of three years' labours,”—when a paper by Valentiner, in the same Archiv, caused me to change my opinion for a very different one. The statements of Valentiner, coupled with the intrinsic evidence contained in the paper of Schottin, have satisfied me that Schottin cannot be believed. Schottin has made no researches on kreatine and kreatinine. His three years' labours, if, indeed, he did undergo any, were directed upon finding allantoin. After Valentiner, in a private conversation, had drawn his attention to his mistake, and told him that the alleged allantoin looked very much like kreatinine, he did not straightforwardly condemn his so-called researches, and start afresh, but he simply substituted the words kreatine and kreatinine for the word allantoin wherever it occurred in his manuscript, and sent the article to press.

Parkes, therefore, unduly questioned my observations of the physiological quantity of kreatine and kreatinine excreted by two healthy men. So far from placing it too high, I have actually given reasons why the quantities which I have found were only expressive of a minimum, and did probably not represent the whole amount of these substances present in the urine analysed. The researches of Neubauer, quoted in the text, have fully borne out my anticipations and analyses.

I preserve a quantity of almost white chloride of zinc kreatinine, which I obtained in the researches first published in the first edition of this treatise, p. 126, *et seq.* Although it has been purified by decomposition and reprecipitation, a proceeding which entails considerable loss of substance, it nevertheless yet amounts to 150 grains, and fills the space of a fluid ounce. What a criticism of Schottin's “microscopical traces” and Parkes's doubts! (“Transactions of the Medical Society of London,” 1862, 2, 104, footnote to an article on Azoturia).

CHAPTER IX.

REDUCINE, $C_6H_{11}N_3O_4$.

HISTORY AND LITERATURE.

THIS alkaloid was discovered by the author in 1874, and first described in Report of the Medical Officer of the Privy Council, new series, No. VI. p. 211, 1875.

Isolation of the Alkaloids contained in Human Urine.

Fresh healthy human urine was shaken with a little animal charcoal to collect the mucus and epithelial elements, filtered, strongly acidified with sulphuric acid, and then precipitated by phosphomolybdic acid. The collected precipitate was washed with water containing a little sulphuric acid. It was then decomposed with hot baryta-water in slight excess; this excess was removed by carbonic acid and boiling, and the filtrate evaporated to a small bulk. On cooling it formed a deposit, which was proved to be *pure urate of baryum*. It was specially proved that it contained no hypoxanthine. The yellow filtrate contained much urochrome, giving on decomposition with hydrochloric acid and boiling uromelanine, uropittine, and evolving smell of omicholic products. It was therefore treated with neutral lead acetate, after this with tribasic lead acetate, and ultimately with this and some ammonia. The united precipitates were further treated as will be stated below. The filtrate from the lead precipitates was freed from excess of lead by hydrothion and concentrated; it was now free from urochrome, but contained yet two alkaloids, of which one was *kreatinine*, the other an alkaloid hitherto unknown, and to which, on account of its remarkable chemical properties, I give the name of *reducine*.

The lead precipitates were united and decomposed by hydrothion. The first watery filtrate was strongly yellow, and on concentration and cooling-deposited pulverulent *xanthine*. This was separated from urochrome by filtration, redissolved in boiling water, identified by argentic nitrate test in nitric acid solution, and combined with silver oxide by treatment of the nitrate salt with excess of caustic ammonia. Filtered, redissolved, and

reprecipitated, and burnt, 0.484 grm. dried at 100° gave 0.251 grm. Ag equal to 51.85 per cent.

A salt $C_5H_4N_4O_2 \cdot Ag_2O \cdot 2H_2O$, would yield 51.4 per cent. Ag. The salt without the two molecules of water requires 56.2 per cent. Ag.

The lead sulphide was further extracted with large quantities of alcohol of 85 per cent., which on concentration to a small bulk deposited much xanthine, and left urochrome in solution. This urochrome solution was united with the main quantity previously extracted by water. The mixture was proved to be *free from chlorine*, and *free from reducin*. It was now evaporated in vacuo over sulphuric acid, treated with alcohol to separate the xanthine as much as possible, filtered, and the alcohol evaporated. The residue was treated with hydrochloric acid, and yielded *uromelanine* and *uropittine* with all their well-known properties. The presence of omicholine was doubtful.

The mother-liquor from these bodies, suspected to contain some xanthine, was treated with phosphomolybdic acid, and the precipitate obtained was decomposed with baryta. The product dissolved in nitric acid, was precipitated from this by silver nitrate; the compound dissolved in excess of nitric acid on heating, was precipitated from this by excess of ammonia, and *redissolved in a great excess of ammonia*, leaving only some slight impurity undissolved. The solution was boiled to expel the excess of ammonia, and the precipitate which fell during the boiling was isolated, and the silver contained in it determined.

0.039 grm. left 0.0174 grm. Ag = 44.162 per cent. This compound therefore contained much less silver than the theoretical xanthine compound, or the compound analysed above. On combustion, too, it behaved differently from the xanthine compound; for it swelled up, and left a cone of spongy metal, while the xanthine salt burns quietly without swelling up, and leaves a nearly white metallic residue.

Reducin.—The filtrate from the lead precipitates described above, as containing this substance and kreatinine, was freed from lead by hydrothion, and evaporated to dryness while being stirred on the water-bath. The residue was treated with boiling absolute alcohol, and the decoction filtered hot. A voluminous baryum salt remained on the filter, while a yellowish matter dissolved in the alcohol. The former was *reducine-baryum*, the latter mainly *kreatinine*.

Reducin-Baryum.—It was easily soluble in water, and after burning left baryum carbonate. On addition to the solution of some nitric acid and silver nitrate a precipitate was produced, which immediately became dark and black in the cold. With mercurous nitrate and nitrite it gave an immediate black preci-

pitate; with mercuric chloride it gave a white precipitate which was not changed by boiling; with cupric acetate and boiling it gave a flaky precipitate which became brown; with Fehling's solution and boiling it gave no reduction.

Analysis of the baryum-compound dried at 100°.

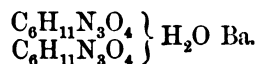
0.4540 grm. gave 0.4520 CO₂ = 27.092 per cent. C. and 0.1750 gm. H₂O = 4.282 per cent. H.

0.2628 grm. gave 33.3 c.c. gas normal = 15.850 per cent. N.

0.4490 grm. gave 0.1940 BaSO₄ = 25.400 per cent. Ba.

		Per Cent.		÷ At W.		÷ Ba = 1.
C	—	27.092	—	2.257	—	12.2
H	—	4.282	—	4.282	—	23.1
N	—	15.850	—	1.132	—	6.0
Ba	—	25.400	—	0.185	—	1.0
O	—	27.376	—	1.711	—	9.2

If the substance be considered as a monobasic acid, these figures lead to the formula—



If it be considered as a dibasic acid they lead to C₁₂H₂₄N₆O₉ as the formula of the free substance. Of this the molecular weight would be 396, while the molecular weight pointed to by the quantity of baryum is 402.

The foregoing figures and formulæ are given with the reserve imposed by the limited quantity of material; but small changes in proportions can detract nothing from the essence of the new facts. The isolation of reducinine has been effected by the application of a reagent of special action on alkaloids. This is the principal proof of the alkaloidal nature of the new body; that it combines with bases after the manner of acids need cause no surprise, as there are many substances known to chemistry which have similar properties; the best known amongst these are the amido-acids, like glykocoll.

Kreatine and Kreatinine.—The alcoholic solution filtered from the *reducine* just described was evaporated, and the residue extracted with little absolute alcohol to remove kreatinine and leave kreatine; the residue was dissolved in hot water, and decolorised by boiling with animal charcoal. It was then allowed to crystallise, and yielded three successive crops of crystals.

First Crystals—Kreatine.—The air-dry crystals had the appearance of kreatine, and their nature was verified by a determination of the water of crystallisation.

0.4596 gm. dried in vacuo over sulphuric acid lost 0.5076 gm. or 12.53 per cent. H₂O. The theory of C₄H₉N₃O₂·H₂O requires

12.08 per cent. The crystals were therefore kreatine. It is known that kreatinine, when freed from its combinations, and particularly in warm baryta water, is easily transformed into kreatine, and these bodies are therefore nearly always obtained side by side in certain proportions.

The second and third crystals were not any further analysed, but assumed to consist mainly of less pure kreatine.

The alcoholic extract supposed to contain the kreatinine was precipitated with alcoholic solution of zinc chloride. The viscous (?) precipitate was freed from mother-liquor by pressure, as far as practicable, redissolved in a minimum of warm water, and reprecipitated by absolute alcohol. Dried over sulphuric acid and ultimately at 100°C ., it constituted a highly electric powder. In this the chlorine was determined by two different methods:—

(a.) By dissolving in dilute nitric acid and precipitating by silver nitrate—

0.5564 gm. dried at 100° gave 0.3660 gm. AgCl = 16.27 per cent. Cl.

(b.) By fusion with caustic soda and nitre, and precipitating solution with silver nitrate—

0.4720 gm. gave 0.3136 gm. AgCl = 16.43 per cent. Cl.

The compound was therefore not a kreatinine salt, which requires 19.6 per cent. Cl. This was further confirmed by the determination of the zinc (in the nitric acid mother-liquor from analysis (a) after removal of the excess of silver by hydrochloric acid), as carbonate in the usual manner. There were obtained 0.1640 gm. ZnO , equal to 23.15 per cent. Zn. The kreatinine salt would require only 17.83 per cent. Zn.

After drying, the body did not completely redissolve in water, but left white flocks insoluble. The filtrate left on evaporation an uncrystallisable salt, mixed with crystals, which were separated by their insolubility in little cold water. The dissolved amorphous body gave with ferric chloride a precipitate, which was permanent on boiling, and thereby reminded of the behaviour of the bodies of the kryptophanic group of extractive acids.

The phosphomolybdic acid process is thus shown to remove from urine several alkaloids, of which one at least is new, *reducine*; another body, *urochrome*, now shown for the first time to be an alkaloid; *xanthine*, known to belong to the class of organic bases; *kreatinine*, also known and mostly obtained as kreatine; and two not yet well characterised bodies, of which the one forms a silver compound, the other a zinc salt, and is precipitated by ferric chloride.

The physiological quantities of these substances are probably not so small as one might be induced to believe from the small quantities actually isolated even from considerable quantities of material by the above process; for the phosphomolybdic precipitate is not very insoluble, and consequently much is lost in the voluminous mother-liquors; these had in the first instance to be operated upon without the employment of heat; but evaporation may in future be tried with certain precautions without fear of destroying the substances above described. The phosphomolybdic acid undergoes some reduction in the urine, which becomes deep green from the admixture of blue oxyde to its naturally yellow colour. It is probable that a portion of the reducline contributes to this effect, and after its oxydation escapes the further steps of the process. Then the baryta process is undoubtedly unwieldy, and likely to produce loss, particularly of bodies of the xanthine group. On the whole, however, the process yields a considerable amount of new and useful information, which, when suitably applied hereafter, cannot fail to produce interesting and important practical results.

CHAPTER X.

HIPPURIC ACID, $C_9H_9NO_3$.

HISTORY AND LITERATURE.

ROUELLE, in 1784 ("Journ. de Méd." 40), discovered a peculiar acid in the urine of cows, described its properties and differences from benzoic acid, and showed that it was destroyed during the putrefaction of the urine. Fourcroy and Vauquelin (1778, "Journ. de la Soc. des Pharmaciens à Paris," No. VI. 41, and tom. 14, 123) repeated the observation of Rouelle, and separated the acid from the urine by the addition of hydrochloric acid. They then, for the purpose of purifying it, as they thought, subjected it to sublimation, thus destroyed the hippuric, and obtaining benzoic acid, erroneously declared this latter to be the acid of Rouelle. With the exception of Proust ("Ann. Chim." 14 (1820), 260), who found benzoic acid as a product of the putrefaction of human urine, and of the distillation with acids of the extract of fresh urine, animal chemists did not pay any attention to the subject of Rouelle's observation, until Liebig resumed its study ("Poggend. Ann." 17 (1829), 389), and fully ascertained the peculiarity and chemical character of hippuric acid, as the name indicates, from horses' urine ("Ann. Chem." 12 (1834), 20). Ure (1840, "Med. Chir. Transact." 26) and Keller ("Ann. Chem." 43, 108) showed that benzoic acid, when taken into the stomach, is transformed in the body into hippuric acid, and excreted as such. Liebig ("Ann. Chem." 50, 161) next proved that it was a normal ingredient of the urine of man; and the observation of Ure and Keller found a parallel in that of Dessaignes ("Compt. rend." 21, 1224), who effected the formation of hippuric acid from benzoic acid and glykocoll by chemical synthesis.

Occurrence.

Hippuric acid is a regular ingredient of the urine of man, the herbivorous mammals, such as the horse, from which it takes its name, horned cattle, camels, elephants, goats, sheep, hares, and rabbits. It is found in guano, the excrements of sea-birds, as hippurate of ammonium, and has been repeatedly observed in the excrements of the Greek tortoise.

Modes of Obtaining it Pure.

1. *From human urine.* Fresh urine is treated with milk of calcined magnesia, filtered and evaporated in the water-bath to a syrupy consistence. The residue is worked into a bottle which can be stoppered, and after the addition of some hydrochloric acid is shaken, with at least an equal volume of ether, which dissolves the hippuric acid. When the extract of the urine was rather fluid, the mixture does not separate, because the ether is enclosed in the fluid, the whole forming a kind of emulsion. But the separation of the ether can mostly be effected, if, after the mixture has stood for an hour, one-twentieth of its volume of alcohol be added. In that case the froth disappears, and the fluid separates into two layers, of which the upper and lighter one contains the hippuric acid; but at the same time there is some urea dissolved in it by means of the alcohol which has been added. This layer is now carefully removed by means of a syphon, and shaken with small portions of water; the alcohol and urea combine with the water, and the hippuric acid, together with some colouring matter, remain dissolved in the ether. By evaporation the acid is obtained in crystals, which generally are of a yellowish or brown colour, from a resinous substance, which may be removed by animal charcoal.

If, however, the extract of the urine was of the proper consistence, it will, after shaking with ether, generally subside to the bottom of the glass after a short time of standing, and the ethereal solution will float on the top, and not require the addition of any alcohol. It may be removed by a syphon fixed in the perforated cork of a flask, so as to admit of being filled by suction at another bent tube inserted by the side of it. The ether in the flask is distilled off, and the fluid residue poured into a small glass, and mixed with some water. After some standing, and in some cases almost immediately, hippuric acid is deposited in silky needles. If a large amount of hippuric acid is present, the fluid is sometimes transformed, on the addition of water, into a solid mass of silky crystals.

After sufficient time has been allowed for the crystallisation of the acid, it is put on a small filter and washed with cold water. By redissolving it in water, and boiling it with some animal charcoal, it is obtained after evaporation crystallised and pure.

When it is intended to obtain the whole of the hippuric acid contained in any given quantity of urine, the extract, after its last remnants on the evaporating dish have been washed into the bottle by means of the hydrochloric acid, must be shaken with its bulk of ether from six to twelve times. Although in most cases five or six applications of ether will be sufficient, in a minority of

cases the extraction of the acid is not completely effected thereby. It is therefore necessary to repeat the extraction with ether until the residue, after evaporation, does not any longer yield any crystals.

2. *From the urine of horses or cows* the acid may sometimes be obtained in the form of a yellowish-brown powder, by the addition of hydrochloric acid. Riley ("Journ. Chem. Soc." 5, 97) recommends to add 6 per cent. of this acid to the urine, as he has found that hippuric acid is much less soluble in strongly acid than in slightly acidulated fluids. This proceeding is quite satisfactory when applied to the urine of animals fed upon grass. Krant ("Henneberg, Journ. f. d. Landwirtschaft," 6 (9), 483, and Chem. Centr. Blatt, 52, 1858) examined the urine of cows which had been out to grass during the morning from 8 to 11, had then been milked in the shed and fed upon some maize straw. At two o'clock their urine had an acid reaction, and on addition of hydrochloric acid, yielded so considerable a precipitate, that from 120 pounds of urine, upwards of one pound of raw hippuric acid was obtained. It is, however, not so with the urine of animals fed upon clover or grains. In this latter case it is preferable to concentrate the neutralised urine to one-sixth or one-eighth of its original volume before adding hydrochloric acid.

The crystals so obtained have got a brownish colour and a disagreeable resinous odour, which must be removed by a purifying process. The solution in water is boiled with some caustic lime and filtered; to the filtrate chloride of lime is added until the urinous odour has disappeared. Animal charcoal is now mixed with the fluid until the filtrate is colourless; the filtrate is mixed with hydrochloric acid, and, on cooling, deposits hippuric acid, perfectly white and pure (Liebig).

The following process for purifying coloured hippuric acid has been described by Gössman ("Lieb. Ann." 99, 364):—The raw material is recrystallised once from boiling water. The crystals are then dissolved in a sufficient quantity of dilute caustic soda, the solution is heated to one moment's ebullition, and a solution of permanganate of potash is added drop by drop, until a small quantity of filtered solution is precipitated white by hydrochloric acid. The entire solution is then filtered from the oxyde of manganese, and yet hot treated with a slight excess of hydrochloric acid. On cooling, pure hippuric acid crystallises.

3. Dessaignes prepares hippuric acid as follows:—Urine is concentrated and allowed to stand for twenty-four hours. It is then decanted and precipitated cold by hydrochloric acid. The crystalline mass is placed upon a funnel and allowed to run off its mother-liquor, and is worked and compressed with a glass rod until it has become very firm. It is then washed quickly until it has only a violet colour. It is purified by boiling with

animal charcoal, and crystallises pure on evaporation ("Journ. d. Pharm," (3), 32, 44).

4. The same author relates in the same place a new mode for obtaining hippuric acid by synthesis. He enclosed equivalents of benzoic acid and glykokoll in a sealed glass tube, and kept the mixture during twelve hours at a temperature of 160° C. The contents of the tube, treated with boiling water, left a white tasteless powder, which was only partially soluble in potash; and from the solution filtered hot, there crystallised, on cooling, a quantity of hippuric acid, which corresponded to two-thirds of the benzoic acid employed.

Other and less productive modes of synthesis of hippuric acid have been formerly described by the same author. The transformation of benzoyl-compounds into hippuric acid within the animal economy belongs to the same category of synthesis, and can be made use of for the purpose of producing hippuric acid for experiment.

Physical Properties.

Pure hippuric acid, prepared from human or animal urine, appears in long, glistening, transparent prisms, four-sided parallel to the longest axis, the ends acuminate by two or four planes, being planes of prisms parallel to the brachy- and macro-diagonal. The primary form is a vertical rhombic prism, whose planes are inclined at an angle of $94^{\circ} 50'$. The planes of the brachy-diagonal (horizontal) prism are inclined at an angle of $94^{\circ} 50'$, those of the macro-diagonal (also horizontal) prism at an angle of $85^{\circ} 14'$. An alcoholic solution of hippuric acid, abandoned during some months to spontaneous evaporation, deposits the acid in granules resembling the tops of cauliflowers.

Chemical Properties.

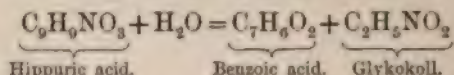
The acid is destitute of odour, and is of a bitterish taste. It requires for solution 600 parts of water of 0° C. temperature, and 400 parts of water at the ordinary temperature of the air; but is much more soluble in hot and boiling water, and in alcohol. Its solubility in ether is somewhat less than in alcohol. The solutions redden litmus paper.

Decompositions.

Hippuric acid is not volatile at the temperature at which benzoic acid sublimes. At a higher temperature it fuses, forming a brownish-red liquid, which on cooling becomes a milk-white crystalline mass. By dry distillation it yields a red oil, with an aromatic odour, ammonia, and benzoic acid (the latter two perhaps in part as benzoate of ammonium), and a large resi-

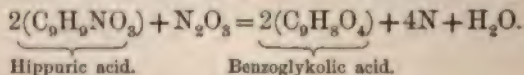
due of charcoal. Sometimes the acid before charring evolves a cyanogen compound, having the odour of hydrocyanic acid. If the temperature during dry distillation be not raised above 250°C ., benzoic acid is obtained, slightly reddened, a trace of hydrocyanic acid, and benzonitrile is collected in the receiver.

Hippuric acid is soluble in warm nitric acid and hot hydrochloric acid, and from both solutions crystallises on cooling; but when boiled for some time in either of these solutions it undergoes a decomposition, by which benzoic acid crystallises out of the solution on cooling. Combined with the nitric acid there remains glykokoll. This decomposition may also be produced by sulphuric and oxalic acids, and by boiling with caustic soda and potash. It can be represented by the formula—



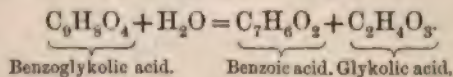
Under the influence of a ferment, in the presence of an alkali, hippuric acid undergoes the same decomposition into benzoic acid and glykokoll. The disintegration of hippuric acid in putrefying urine is thus satisfactorily explained.

Hippuric acid can also be considered as the amide of benzoglykolic acid, which is free from nitrogen, and has the composition $\text{C}_9\text{H}_8\text{O}_4$. It is formed when hippuric acid is acted on by nitrous acid, and is obtained by conducting a current of nitric oxyde through a solution of hippuric acid in nitric acid—



Benzoglykolic acid crystallises from the solution in colourless prisms, which are easily soluble in alcohol and ether, but sparingly soluble in water. It forms neutral salts with one molecule of base, which are mostly crystallisable. The lime-salt, $\text{C}_{18}\text{H}_{14}\text{CaO}_8$, crystallises in colourless needles, and has a tendency to form oversaturated solutions.

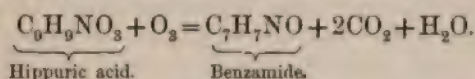
When benzoglykolic acid is treated with dilute acids it is decomposed to benzoic and glykolic acid after the formula—



This decomposition explains why hippuric acid, although it be the amide of benzoglykolic acid, does not yield that acid and ammonia when boiled with acids, but benzoic acid and glykokoll. The benzoglykolic acid is at first formed along with ammonia, but is immediately decomposed into benzoic and gly-

kolic acid, and the latter, with the ammonia, forms its amide, glykokoll, and water.

Hippuric acid, when boiled with peroxide of lead in water, yields benzamide, carbonic acid, and water, according to the following formula (Fehling, "Ann. Chem." 28, 48):—



Reaction for Hippuric Acid.—Horsford's reaction for glykokoll, a red coloration when thrown upon fused potash, succeeds also with hippuric acid. The potash must be heated very little above its fusing point, and only so much as to be still a monohydrate (Dessaignes).

Compounds of Hippuric Acid.

Nitrohippuric Acid, C₉H₈N₂O₆.—To a solution of hippuric acid in cold fuming nitric acid, an equal volume of oil of vitriol is gradually added, care being taken not to let the mixture get hot. After two hours the reaction is completed. The fluid is now mixed with three times its volume of water, being continually kept at a low temperature. The mixture, after twelve hours, has deposited about one half of the hippuric acid employed in the form of nitrohippuric acid in needle-shaped crystals. The mother-liquor, when neutralised by carbonate of soda until it begins to get turbid, deposits another quantity of the acid. The impure acid is washed with cold water, combined with lime, and the solution of the lime-salt in lukewarm water is precipitated by hydrochloric acid.

Nitrobenzoic acid may be taken internally, in quantities amounting to 6 grammes per diem, without injury to the body. It reappears as nitrohippuric acid in the urine, from which it may be obtained by the following proceeding:—The acid urine is evaporated to a small bulk. It remains clear on the addition of hydrochloric acid; the fluid is now shaken with ether and some alcohol, which take up nitrohippuric acid, and, on spontaneous evaporation, deposit it in brown warty crystals, which, when removed from the mother-liquor, dried on a brick, and recrystallised from hot water, appear as brownish needles. When boiled for five minutes with excess of milk of lime, colouring matter is removed, and the filtrate, on decomposition by hydrochloric acid, yields pure nitrohippuric acid, which is obtained in fine crystals by recrystallisation from hot water.

Hippuric Acid Salts—Hippurates.

These salts have been studied by Schwartz ("Ann. Chem." 54, 29).

The alkaline and earthy hippurates are soluble in water. Hippurate of sodium seems to be a combination which occurs in human urine. But as hippuric acid in human urine, when present in larger quantities, crystallises on simple evaporation on the surface of the fluid, it is probable that it may also be present in the free state. In the urine of the horse hippuric acid is combined with calcium. Metallic hippurates are sparingly soluble. All hippurates yield their bases to hydrochloric acid, hippuric acid crystallising from the solution in delicate silky needles.

The hippurates may be basic, neutral, or acid salts; that is, containing either one-half, or one or two molecules of acid to one of base.

Hippurate of Baryum, neutral, $C_{12}BaH_{16}N_2O_6 + H_2O$.—By dissolving hippuric acid in excess of baryta water, and precipitating the excess of baryta by a current of carbonic acid, or by boiling an excess of carbonate of baryum in a solution of hippuric acid, a solution of neutral hippurate of baryum is obtained after filtration, which on evaporation yields the salt in crusts, consisting of microscopic quadratic prisms.

Hippurate of Calcium, $C_{12}CaH_{16}N_2O_6 + 3H_2O$.—By boiling an excess of carbonate of calcium in a solution of hippuric acid a filtrate is obtained, which on evaporation deposits this salt in rhombic prisms or glistening scales. It is also obtained by boiling a solution of hippuric acid with excess of milk and lime, filtering, and passing a current of carbonic acid gas through the solution. The filtrate contains the salt. This compound is said to occur in the urine of the horse and cow. It is soluble in 18 parts of cold and 6 parts of boiling water.

Hippurate of Lead, neutral, $C_{12}PbH_{16}N_2O_6 + 3H_2O$, is obtained by mixing the hot solution of an hippurate with solution of acetate of lead; on cooling the salt is deposited in laminae of the lustre of mother of pearl. If cold solutions of lead and hippurate are mixed, the salt precipitates at once in cheesy flakes, which are with difficulty soluble in boiling water. The precipitate may be washed on a filter, dissolved in boiling water, and after filtration while boiling hot, on a funnel, kept hot, is obtained from the cooling solution in silky groups of fine needles. These needles contain only two molecules of water of crystallisation, but frequently transform into the salt with three molecules of water, by suddenly taking up one more molecule of water under circumstances not yet accurately known. A basic hippurate of lead is obtained by boiling hydrated oxyde of lead in a solution of hippuric acid.

Hippurate of Iron.—The soluble hippurates cause a rusty brown precipitate in salts of the oxyde of iron. Neutral sesquichloride of iron produces a light fawn-yellow voluminous preci-

pitate in a cold solution of hippurate of potassium, which in hot water, or by drying at a temperature of 30° C., loses water, and forms a brown mass. It is insoluble in water, easily soluble in spirit of wine, particularly in hot spirits, and from the solution separates on cooling, partly in amorphous masses, partly in groups of red oblique rhombic prisms.

The salts with cobalt, nickel, copper, mercury, and zinc present no striking peculiarities. The silver salt is distinguished by containing a molecule of water of crystallisation; while the silver salts of most other organic acids are free from water of crystallisation.

Physiology.

Benzoic acid introduced into the stomach appropriates to itself glykokoll, and appears in the urine as hippuric acid. From this fundamental observation of Ure, confirmed as it was by Keller, numerous inquiries have been started, and established the existence of a kind of physiological law, that benzoyl-compounds, however varied may be the substitutions among their looser component elements, will in the body undergo the same transformation as benzoic acid, and appear in the urine as hippuric acid. Thus benzoic ether, benzoyl-hydride, cinnamic acid, all yield the same final product; their outer radicals are destroyed or otherwise disposed of in the economy, while their benzoyl, apparently indestructible by animal oxydation, reappears with glykokoll in the excretion.

This phenomenon soon suggested to inquirers the probability that all hippuric acid contained in either the urine of animals or of man was but the product of the transformation of some compound of benzoyl contained in their food. They therefore directed their inquiries towards the proximate ingredients of the mixed food of man and the fodder of animals. From the ordinary mixed food of people accustomed to good living, no benzoic acid could be extracted. The urine of cows was said to be always equally rich in hippuric acid, whether they fed on mangelwurtzel, grass, or hay. It was known from the exact experience derived from the manufacture of sugar from beetroot, that this vegetable did not contain any benzoic acid. Hallwachs ascertained, by an examination of the fodder of a cow, which yielded largely hippuric acid, that the plants constituting the fodder did not contain either benzoic acid, or any benzoyl-compound, in such a form that it could be extracted by ordinary analytical means. The conclusion appeared, therefore, for a time inevitable, that the benzoic acid contained in the hippuric acid in the urine of animals, whose food does not contain any benzoyl-compounds as proximate constituents, must be a product of the organism, towards the formation of which the food only furnishes the elements.

But the value of this conclusion was soon modified by the accidental discovery, that among the fruits of the earth enjoyed by man as food there is at least one which contains benzoic acid in such quantities as to materially affect the composition of the renal excretion in persons who have partaken of even a moderate quantity of it. Ducheck ("Prager Viertelj." (1854), 3, 25), in the course of some determinations of uric acid by precipitation with hydrochloric acid, one day encountered a mass of crystals, which he recognised as hippuric acid. He had the day before eaten fruit, luckily new to him, being however nothing more uncommon than a number of greengages. He then repeated the eating as an experiment, and found it to have the supposed effect. The urine passed after the ingestion of a number of greengages was so saturated with hippuric acid, that after the simple addition of hydrochloric acid in the cold, the acid crystallised in long silky needles. He then directed his researches towards the greengages themselves, and found them to contain a quantity of benzoic acid. But the quantity of benzoic acid which they yielded to extraction was never so large as that which an equal quantity of the same fruit would yield in the form of hippuric acid when ingested into the stomach of the experimenter. He therefore concluded that the greengage, besides benzoic acid accessible to analysis, contained other benzoyl-compounds not so easily revealed in extracts, amongst them perhaps benzoic ether and benzoyl-hydrogen, and determined the amount of benzoyl contained in them physiologically, that is to say, by passing given quantities through the ordeal of the chemistry of his body. 840 grammes of greengages without stones, eaten, yielded 3.736 grammes of hippuric acid, containing 2.021 grammes of benzoic acid. 403 grammes of greengages without stones, eaten, yielded 2.920 grammes of hippuric acid, containing 1.990 grammes of benzoic acid. Calculated for 100 parts, the first greengages yielded 0.252 per cent. of benzoic acid, the second 0.493 per cent., which gives an average of 0.3715 per cent. of benzoic acid in greengages. Apples, pears, and common plums never produced any effect like the greengages. The excretion of hippuric acid began seven or eight hours after the eating of the fruit, and was always completed in from three to five hours later.

My own researches have confirmed this observation of Ducheck. Greengages, in whatever form or quantity taken, always increased the amount of hippuric acid in the urine far beyond what it was under ordinary mixed diet, containing no ingredient that could be said to harbour any benzoyl-compounds. It was therefore clear that if the human economy produced any benzoic acid from the elements of assimilated food, another quantity of this acid might be introduced into the body as such by the ordinary accidents connected with the variations of food. It was also evident that any inquiries into the quantities of hippuric acid

discharged in given times by healthy and sick individuals would have but little significance, unless the nature as well as the quantity of the food eaten was taken into consideration. Physiological researches which did not observe these precautions could answer only very few questions. The bearing of the answer under any circumstances was more upon the uncertain element of the nature and amount of food taken, than upon any peculiarity in the processes of the animal economy.

If the hippuric acid is a normal ingredient of human urine, and its variable portion is due to the introduction into the economy of benzoyl-compounds contained in food, such as green-gages, the more stationary amount of it must be derived from the elements of food, or from certain radicals contained in food, and appearing as benzoyl only after complete destruction by oxydation. Such a radical is perhaps contained in albumen and other substances deriving therefrom, as was made probable by the observations of Proust (Gehlen's "Neues Journ. d. Chem." 2, 241), afterwards confirmed by Guckelberger ("Ann. Chem." 64, 39), that oil of bitter almonds and benzoic acid were among the products of the oxydation of albuminous substances by bichromate of potash and sulphuric acid. We may, therefore, think it possible that the oxydation of albuminous substances in the body is effected in an analogous manner, and may yield benzoic acid as a collateral product in small quantity, to be afterwards combined with glykokoll, or that the simultaneous production of benzoic acid and glykokoll results in the direct formation of hippuric acid. The sources of the glykokoll which combined with any benzoic acid introduced into the body, have always appeared less problematical than those of the benzoic acid contained in the regular hippuric acid. The bile might easily yield it if the glykocholic acid was really split up in the manner indicated by its chemical decomposition out of the body. Indeed, this origin has been claimed as proved by W. Kühne and W. Hallwachs ("Nachr. d. Kön. G. d. Wiss. zu Göttingen," 11 Mai 1857, p. 129-134), who performed the following experiments:—Having ascertained that a dog transformed benzoate of soda, which was given to it in its food, into hippurate, they injected various quantities of benzoate, corresponding to from 1 to 4 grammes of acid, into the veins of dogs and cats. In about 20 experiments the benzoate was excreted in the urine almost entirely unchanged. When the salt was given with its food to a dog, whose bile was entirely evacuated by a fistula, no trace of benzoic acid appeared in the urine, which contained, however, hippuric acid. But no trace of hippuric acid was discharged by three cats which had taken benzoic acid, and whose entire liver had been ligatured in such a manner as to prevent blood and bile from either entering or leaving. These latter experiments can

hardly be admitted to demonstrate anything, as the interference with all vital functions caused by a ligature round the base of the liver must be so enormous as to prevent just that kind of action in the entire economy which would be required to form hippuric acid anywhere. Indeed, these experiments were only undertaken to save the hypothesis which had been defeated by the previous experiments, in which the entire abstraction of the bile did not prevent the transformation of benzoic into hippuric acid. On the whole, the experiments show that the transformation is probably effected in the intestinal canal; that the bile is not essential to it; that other products of the decomposition of the food in the intestinal canal can furnish the glykokoll, and that the blood by itself does not furnish the glykokoll or allow its combination with benzoic acid to take place within the limits of the circulation.

According to Ducheck ("Prager Viertelj," (1854), 3, 25), only a limited amount of benzoic acid can in a given time be transformed into hippuric acid. He found in the urine—

				Acids	
				Hippuric.	Benzoic.
When 1	gram.	of benzoic acid	had been taken,	0.714	0.000
"	2	grammes	"	1.857	0.421
"	4	"	"	1.714	2.500

so that while in all experiments there was a considerable loss of benzoic acid unaccounted for, in the last experiment more than half of the benzoic acid taken apparently escaped unchanged through the kidneys. Similar experiments instituted by Piotrowsky led to results which were averse to Ducheck's conclusions, and seemed to indicate that even larger amounts of benzoic acid, up to ten and twelve grammes, are entirely transformed into hippuric acid during their passage through the body. Peculiarities of diet may perhaps hereafter furnish as unexpected a solution of the question after the origin of glykokoll, just as they have supplied an answer to the question after the sources of a part of the benzoic acid.

The urine of carnivorous animals has not been observed to contain any hippuric acid. But as we are not acquainted with any direct researches on the subject, it is unadvisable to rely upon this circumstance for any further conclusion.

Regarding the physiological bearing of hippuric acid in horses and cows, the observations at one time seemed to show that rest and activity, as well as different descriptions of food, had a considerable influence upon the quantity in which it is found in the urine. Erdmann ("Journ. f. pr. Chem." 13, 422) asserted that some of these circumstances could cause a substitution of benzoic for hippuric acid, that, therefore, benzoic acid could

temporarily be a normal ingredient of the urine of these animals. The urine of six horses used for ploughing gave one day benzoic, the next day hippuric acid, there being no change in the diet. He communicated this experience to Liebig, who replied that he had observed the same occurrence, and expressed a belief that evaporation of the urine at too high a temperature had an influence in the matter. This latter also observed that there might be a peculiar ferment in some description of urine which might decompose the hippuric acid quickly. He had formerly ("Ann. Chem." 30, 280) communicated the opinion that any benzoic acid found in the urine of horses was the product of putrefactive changes. At a later period ("Ann. Chem." 41, 272) he stated an opinion, perhaps in part derived from the unexplained experience of Erdmann, that horses and horned cattle, during the normal state of activity and work discharged urine containing principally benzoic acid, but that when the animals were quiet in the stables they excreted hippuric acid. The animals were explained to get rid of a highly-carbonised material during rest by the kidneys, which during work they used for the production of power, and excreted by the lungs as carbonic acid. This explanation inspired Erdmann (in the article which he published, in conjunction with Marchand, on the transformation of cinnamic into hippuric acid in the human body ("J. f. Pract. Chem." 26, 492), to formularise his singular experience into a general doctrine, to the effect that horses kept for pleasure, and which, consequently, were well fed and little exercised, yielded much hippuric, but horses used for ploughing only, benzoic acid. After that it was not surprising that Hutstein ("Brandes. N. Archiv. d. Pharm." 66) should also have observed that the urine of horses which while working moderately had only yielded hippuric acid, contained only benzoic acid after they were used for hard work.

In direct contradiction to the above statements on the substitution of benzoic for hippuric acid, by certain alterations of activity and diet, stand the observations of Lehmann ("Handwörterbuch der Physiologie," p. 14). He examined the quite fresh urine of a very large number of both well and badly-fed, healthy and sick horses, and found it always to contain only hippuric and no benzoic acid. But when the urine had been allowed to stand for some time exposed to the air it always contained only benzoic acid. Such fermented urine infected fresh urine, to which it was added so very rapidly that the hippuric acid was, during mere evaporation of the fluid, entirely decomposed, and nothing but benzoic acid was left. If, then, the chemists who found benzoic acid in the urine of working animals did not collect the excretion in such a manner as to protect it from contact with the stale urine on the floor and in the

gutters of stables (which, while the horses were at work, would be less frequently renewed, and consequently more infected or decomposed), or did not work it up quickly while it was in a fresh state, they omitted a precaution, without which their results are open to question.

The influence of some descriptions of food upon the hippuric acid in the urine of animals has been investigated by various observers. Landerer ("N. Journ. d. Pharm." 20, 288) found that the urine of horses would yield hippuric acid while they were fed on oats and hay, and did not yield any while fed on barley and straw. That the hay had the principal share in the production of hippuric acid in Landerer's horse is evident from the experience made upon cows feeding on grass, and from the following observation of Städeler ("Ann. Chem." 77, 39):—He found in the morning urine of a horse, which was almost entirely fed upon oats, and seldom was in the stable during as much as a day, only traces of hippuric, and no benzoic acid. Riley also ("Journ. Chem. Soc." 5, 97) found the urine of cows to yield hippuric acid only while feeding on grass or hay; and Schwartz ("Ann. Chem." 54, 31) observed that the urine of cows contained only traces of hippuric acid when fed on the residue from the distillation of spirit from fermented potatoes. Kolbe ("Lehrb. d. Organ. Chem." 2, 113) observed that the urine of cows which had for some time yielded a considerable amount of hippuric on addition of hydrochloric acid, suddenly ceased to do so. On inquiry it was ascertained that from the day when the urine ceased to give hippuric acid the cows had been fed upon clover instead of grass, as before. These observations, no doubt, militate against the opinion of Hallwachs, and make us inclined to believe that grass contains substances capable of forming hippuric acid, which are wanting in clover, oats, and distillery refuse. Kolbe did not examine the urine of the cows fed upon clover any further, in order to ascertain the degree of diminution which the quantity of hippuric acid had undergone. Wanting this precaution, his observation can only be admitted to show that the urine of cows contains relatively less hippuric acid when fed upon clover than while eating grass, at most, that cows fed upon clover secrete less hippuric acid than cows eating grass.

Quantity of Hippuric Acid Secreted in Twenty-Four Hours.

It had been stated by Liebig that hippuric acid was present in human urine in about the same proportion as uric acid. This opinion was generally received until Hoefle and Ducheck negated that hippuric acid was a constant constituent of human urine. Subsequently Hallwachs ("Ann. Chem." 105, 207, and 106, 160) found the amount of hippuric acid in the urine of some persons to be nearly one gramme in 24 hours. About the

same time Weismann (Henle and Pfeuffer, "Zeitschr. f. Rat. Med." (3), 2, 332) instituted some experiments upon this subject, which consisted in observations of particular diet, measurements of the urine discharged, and attempts to determine the amount of hippuric acid contained therein, by evaporating from 10 to 20 c.c. of urine only, adding five to ten drops of hydrochloric acid to the residue, and extracting it repeatedly with the six to ten-fold volume of ether. The coloured residue was assumed to be hippuric acid. There can, however, be no doubt that this residue contained colouring matter removable by water, urea, and other matter. No experiment seems to have been made to ascertain the amount of impurity mixed with the acid obtained. These circumstances make the results of Weismann inadmissible for comparison with the results of other observers; only by their differences amongst themselves they indicate a few physiological conclusions, such as that the amount of hippuric acid in human urine is greater after mixed than after animal diet; that pure bread diet reduces the quantity of hippuric acid below that yielded by animal diet, and that in acute inflammatory or zymotic diseases, such as pneumonia and typhus fever, the amount of hippuric acid in the urine sinks below that obtained under the influence of bread diet. Still larger than the quantities obtained by Weismann, and arrived at by a still more fallacious proceeding, were those given by Wreden ("Bullet. del' Acad. de St. Petersbourg," Classe Phys. Med. 17, 500). He had employed a standard solution of chloride of iron for the determination of hippuric acid, and gave as the average of 29 determinations, 47.4 grains of hippuric acid to the litre (1.7 pints) of urine. The minimum amount found was 32.3 grains, and the maximum 87.8 grains, to a litre. Bence Jones ("Journ. Chem. Soc." (1862), 15, 81) caused some new analyses to be made by Ulrich upon the urine of two healthy men. In these analyses, usually 400 c.c. of urine were evaporated to a syrupy consistence in a water-bath; hydrochloric acid was added, and the hippuric acid was extracted by treating the precipitate with ether four or five times. The first man weighed 10 st. 12 lbs., lived upon a good mixed diet, and took moderate exercise. He excreted in three days the following quantities of urine, and therein hippuric and uric acid:—

	Total of Urine.	Spec. Gr.	Hippuric Acid.	Uric Acid.
1st day,	930 c.c.	1022	6.1 grains.	...
2d "	980 "	1020	4.1 "	8.4 grains.
3d "	790 "	1022	4.7 "	7.1 "
Mean,	900 "	1021.3	4.9 "	7.7 "

The second man experimented upon weighed 14 st. 6 lbs., took

a meat breakfast and good mixed dinner, and took very little exercise. On four days he excreted the following quantities of urine, hippuric, and uric acid:—

	Total of Urine.	Spec. Gr.	Hippuric Acid.	Uric Acid.
1st day,	1460 c.c.	1017	7.3 grains.	14.6 grains.
2d "	1103 "	1019	5.65 "	10.9 "
3d "	1510 "	1017	7.6 "	13.1 "
4th "	1326 "	1019	5.8 "	12.5 "
Mean,	1349 "	1018	6.5 "	12.6 "

Variations of Hippuric Acid in Urine before and after Food.

These variations were determined by Bence Jones in seventeen experiments performed upon the urine of a man who weighed 14 st. 6 lbs., ate a meat breakfast, a good dinner, and took very little exercise. They were found to be somewhat simultaneous with analogous variations in the quantity of uric acid. These determinations were apparently made without reference to any given time during which the urine operated upon was secreted. If the excretion per hour had been determined, as well as the variation in the per centic composition of the urine, the physiological value of the investigation would have been much enhanced.

It follows from these determinations that the hippuric acid was increased, on an average,

From 4.51 grs. per litre of urine before food,
To 5.94 " " after food;

whilst the uric acid was increased, on an average,

From 6.05 grs. per litre of urine before food,
To 9.45 " " after food.

On the whole, it follows that the quantity of hippuric acid, as compared to that of urinary water, rises with the density of the urine, the reverse obtaining in exps. 7 and 9. In some cases (exps. 6, 11, 14, 15, and 16) the relative quantity of hippuric acid is actually smaller after food than before food, while the same relative diminution of uric acid after food occurs more rarely (exp. 7). The rise and fall of the relative quantity of uric acid before and after food, with the specific gravity, is much more true than that of hippuric acid. For while in all experiments, excepted only No. 7, the relative amount of uric acid is increased after food, in the only case where it is decreased the specific gravity is decreased as well, and that considerably (exp. 7, from 1019 to 1014). In exps. 9 and 11 a decrease of the specific gravity coincides with an increase in the relative

amount of uric acid, and in exp. 6 the stationary specific gravity does not prevent the relative rise of uric acid.

*Diurnal Variations of the Quantity of Hippuric Acid
in Human Urine.*

The following researches were made upon the urine of a healthy man, weighing 10 st. 7 lbs., and eating a moderate amount of good mixed diet. He led an active life, and during the inquiry was, on an average, at work during sixteen hours out of the twenty-four:—

1. On August 17th, at 9 o'clock A.M., there had been collected 1370 c.c. of urine from the previous twenty-four hours. Sp. gr. 1017. 200 c.c. treated with hydrochloric acid yielded uric acid 4.1 grains. The whole quantity of urine contained 28.7 gm. of urea, estimated by nitrate of mercury. 500 c.c. were evaporated on the water-bath, treated with hydrochloric acid, ether, and a little alcohol; the extraction was repeated with six portions of ether; the united ethereal extracts were washed with small portions of water, and then reduced by distilling off the ether; the residue was precipitated by a little water, allowed to stand for crystallisation, the crystals were collected on a filter, washed with cold water, dried in the water-stove, and weighed in covered glasses. There were obtained 0.516 gm. of hippuric acid, corresponding to 1.413 gm., as the total amount of acid contained in the whole twenty-four hours' urine. The water with which the ether had been washed was evaporated and set aside for crystallisation; it yielded 0.126 gm. of hippuric acid. This addition swells the calculated amount of hippuric acid in the day's excretion to 1.758 gm.

This analysis demonstrated clearly that the analytical proceeding had to be changed, so as to avoid the loss occasioned by washing with water the ethereal solution containing alcohol. This was effected by evaporating the extract of the urine to a stiff syrup, working it into a stoppered bottle while warm, taking up the last residues with the necessary amount of hydrochloric acid, and shaking briskly with large quantities of dry ether. In this manner the extract and ether separated almost immediately, and required but rarely the addition of alcohol. The ether took up much less urea than it would have done had it contained alcohol. After distillation a small quantity of reddish-yellow residue was obtained, which was mixed with a little water and allowed to crystallise. The crystals were always washed until the washings were colourless, next dried by pressing between blotting-paper, exposure to air, then by keeping over sulphuric acid, and ultimately by drying at 100° C. in the water-oven. This proceeding was carried out in all subsequent examinations.

2. August 18th. 1580 c.c. contained 30 grm. of urea; 200 c.c. yielded 3.1 grains of uric acid; 500 c.c. yielded 0.282 grm. of hippuric acid, corresponding to 0.891 grm. per day.

3. August 19th. 1720 c.c. contained 30.96 grm. of urea; 500 c.c. yielded 1.3 grains of uric acid; 500 c.c. yielded 0.203 grm. of hippuric acid, equal to 0.698 grm. per day.

4. August 20th. 1600 c.c. urea = 28.8 grm.; uric acid, 1.6 grains; hippuric acid in 500 c.c. = 0.178 grm., equal to 0.569 grm. per day.

5. August 21st. 1525 c.c., the whole evaporated for hippuric acid.

The 1st 6 oz. of ether extracted	0.433	} 0.603 grm.
The 2d 6 oz. of ether extracted	0.110	
The 3d 6 oz. of ether extracted	0.060	

There was a firm sediment in the bottle, so that a little hippuric acid may have escaped extraction.

6. August 22d. 1345 c.c. and estimated loss of 155 c.c., total 1500 c.c. The entire amount evaporated for analysis.

The 1st 6 oz. of ether extracted 0.19 grm.

The 2d 6 oz. of ether extracted 0.127 grm. { very pure and
shining crystals.

The 3d extraction with ether and alcohol yielded no hippuric acid.

Total obtained,	0.317 grm.
Add 10 per cent. for loss,	0.0317 grm.

Total in twenty-four hours, . . . 0.3487 grm.

This decrease of the quantity of hippuric acid from the large amount discovered on August 17th, in obs. 1, exciting attention, it was remembered that the experimenter had, on August 16th, eaten some greengage tart at dinner. In order to test whether the large amount in obs. 1 was really due to this cause, he ate twelve hard, scarcely ripe greengages in the evening of the 22d.

7. August 23d. 1470 c.c. The whole evaporated yielded—

On 1st extraction,	0.437 grm.
On 2d extraction,	0.438 grm.
On 3d extraction,	0.162 grm.

Total, . . . 1.037 grm.

On a fourth extraction by 6 ounces of ether, a trace of hippuric acid was still obtained. This, together with the result of the fourth extraction of the residue of No. 6, weighed 0.015 grm. He ate six greengages with tart at dinner, having eaten five after

breakfast. In the evening he ate again six French ones—ripe, slightly bitter.

8. August 24th. 2150 c.c.; loss of 150 c.c. The entire amount evaporated gave—

1st extraction, . . .	1.537 gm.
2d extraction, . . .	0.234 gm.
3d extraction, . . .	0.169 gm.

Total, . . .	1.940 gm.
--------------	-----------

To this must be added the amount of acid lost in the 150 c.c. of urine, which will bring it to upwards of 2 gm.

9. August 25th. 1420 c.c. hippuric acid = 0.450 gm. The second extraction yielded nothing.

10. August 26th. 1670 c.c.

1st extraction, . . .	0.380 gm.
2d extraction, . . .	0.242 gm. very pure.
3d extraction, . . .	0.096 gm. very pure.

Total, . . .	0.718 gm.
--------------	-----------

11. August 27th. 2200 c.c.

1st extraction, . . .	0.360 gm.
2d extraction, . . .	0.056 gm.

Total, . . .	0.416 gm.
--------------	-----------

On the evening of this day the experimenter again ate some greengages.

12. August 28th. 1600 c.c.; hippuric acid, 0.627 gm. It was very dark, and on drying in the water-oven, yielded a sublimate of benzoic acid. The laboratory was filled with the smell of this acid. The experimenter ate again some greengages on this day.

13. August 29th. 2200 c.c.; hippuric acid, first extract, 1.063 gm. There was a little benzoic acid sublimed upon the cover. The second and third extraction yielded nothing.

14. August 30th. 1050 c.c.; of this 800 c.c. evaporated, yielded 0.129 gm. of hippuric acid in fine crystals. Total for 1050 c.c. = 0.169 gm. Second extraction yielded nothing.

15. August 31st. 1450 c.c.; hippuric acid, 1.144 gm. On this day the inquirer ate a pint of greengages.

16. September 1st. The urine from twenty-four hours amounted to 1260 c.c. It yielded a very dark extract, from which 1.405 gm. of hippuric acid were obtained.

17. September 2d. 1860 c.c.; hippuric acid = 1.129 gm. A pint of fine ripe greengages were eaten on this day.

18. September 3d. 1850 c.c.; hippuric acid 2.212 grm.
19. September 4th. 1600 c.c.; hippuric acid 0.507 grm.
20. September 5th. 1780 c.c.; hippuric acid 0.315 grm.

These results clearly show that, while the ordinary amount of hippuric acid excreted by the person under observation may vary between from 0.169 to 0.315 and 1.0 grm., this quantity will be regularly increased after eating greengages, and in proportion to the number or quantity of greengages consumed.

During the evaporation of the urine voided after the eating of greengages, it was observed that some benzoic acid was volatilised, and crystallised on the surface of the paper with which the dish was covered. I am of opinion that this benzoic acid was present in the urine as such.

Variations of Hippuric Acid in Disease.

The case of a girl suffering from chorea, who lived on apples, bread, and water, and discharged a large quantity of hippuric acid, has been recorded by Pettenkofer ("Ann. Chem." 52, 86). The extract of the urine treated with nitric acid yielded a crystallisation of hippuric acid, and only little nitrate of urea. Pettenkofer calculated that the amount of hippuric acid was 12 parts in every thousand of urine, or about one-fourth of the entire amount of solid residue. This is no doubt a very unusual proportion, and can only be accounted for by the circumstance that the girl took little urea-producing food, as she vomited all meat and even broth the moment after she had taken it. Relatively, the urine contained less hippuric acid than that of cows, in whom the hippuric acid frequently rises to 22 and more parts per thousand of urine. There is little doubt that if the origin of the hippuric acid was not in peculiar medicines containing benzoic, toluic, cinnamic, or other similar ingredients, it must be sought in the apples principally, and only to a small extent in the bread and water. Probably the absolute quantity of hippuric acid excreted in 24 hours by this patient was not very large. She exhibited this symptom for a fortnight, when her recovery was so far advanced that she could partake of the mixed full diet of the hospital, whereupon the urea and hippuric acid in her urine assumed the usual proportions.

In a case described by Bouchardat, under the title of "Hippurie," in the "Annuaire de Thérapeutique pour 1842," p. 285, milk diet is blamed as the cause of a discharge of two parts of hippuric acid in a thousand of the urine, by a woman suffering from a variety of severe disorders. Bence Jones met a case in St. George's Hospital resembling the description given of "hippurie" by Bouchardat. The urine was very dilute, of yellowish colour, and feebly alkaline reaction. 420 c.c. of urine contained only traces of hippuric acid. Since we know that greengages

may produce "hippurie," the observation of Bouchardat has lost in pathological significance.

A case observed by Garrod (originally communicated in G. Bird's work on "Urinary Deposits," p. 303) relates to a young man who under certain circumstances discharged a urine which on the addition of an acid yielded crystals of hippuric acid. Half a pint of urine yielded 40 grains of the acid. No information as to the source of the hippuric acid could be obtained from the history of the patient. It is denied that he had ever taken any benzoic acid, so that if no imposition was practised by the patient, and he had not indulged in a considerable amount of greengages or apples containing benzoyl-compounds, there is at all events some mystery about his case.

For many years Lehmann had been teaching that a large amount of hippuric acid was present in the acid urine of fever-patients, of which it was said to cause at least in part the acid reaction. But he offered no quantitative determinations in support of his assertion, and admitted in a general way that relations of certain diseases or groups of symptoms with the quantities of hippuric acid contained in the urine did not exist. Late researches have conclusively shown that this latter view is the correct one, and that the quantity of hippuric acid in the urine in diseases rises and falls simply in a direct ratio to the amount and nature of the food consumed. Weismann examined the urine of seven patients affected with typhoid fever, who had during two or three weeks only taken milk and broth. He found it to yield only one-third or one-fourth of the quantity which his normal urine had yielded him while under the influence of normal mixed diet, but nearly the same amount as other normal urine yielded which was excreted under the influence of purely animal diet.

In a case of acute rheumatic fever observed by Bence Jones, the sp. gr. of the urine was 1010; it had a brown-yellow colour, and acid reaction. 350 c.c. of this urine contained a very small quantity of hippuric acid.

The same author mentions a case of diabetes (sp. gr. of the urine, 1040), 400 c.c. of whose urine examined for hippuric acid yielded only traces of it. Lehmann, who proved the presence of hippuric acid in diabetic urine before it had been found to be normally present in urine, always found hippuric acid in diabetic urine, and in one instance determined its proportion to be 0.025 per cent. This corresponds to about 3.7 grains in the litre, and is less than the proportion found by Bence Jones in urine before food. But considering that the diabetic patient probably discharged a large amount of urine, it is but fair to conclude that he discharged more hippuric acid in 24 hours than other healthy persons of similar age and weight. Should this surmise be con-

firmed by analyses, undertaken with due regard to the time in which the urine is discharged, the information would still be only confirmatory of what we may hold *a priori*, namely, that the increased amount of hippuric acid discharged daily by diabetic patients is the result of an increased consumption of benzoyl-compounds in the very large amount of food which they are by their peculiar indisposition compelled to consume.

Kühne (Virchow's "Archiv," 14) had examined the urine in cases of closure of the common bile-duct, and been unable to find any hippuric acid in it. This circumstance served as a support of his doctrine that the presence of glykocholic acid in the intestines was an essential condition of the formation of hippuric acid. In opposition to this assertion were the results of Neukomm (communicated in Frerichs, "Klinik d. Leberk." 2, 537), which stated icteric urine to contain hippuric acid whether benzoic acid had been taken or not. The inquiry was lately resumed by Schultzen (Reichert's "Archiv." 1863, p. 204), and the contradictions explained in a satisfactory manner. He examined the urine of a man who for eight months had been suffering from icterus. 500 c.c. yielded, after evaporation by itself, without any previous preparation, only benzoic acid. No hippuric acid could be found. The patient then had a drachm of benzoic acid, saturated with soda given to him between the hours of three and nine P.M. All urine collected up to next day yielded only benzoic, and no hippuric acid. The patient now took another drachm, and the urine after collection was immediately treated with acetate of lead, so as to remove those changeable matters which are capable of acting as ferments. The extract now yielded a large amount of hippuric and no benzoic acid. It was, therefore, evident that in this case of jaundice from occlusion of the common duct, the benzoic acid was transformed in the same manner as in health, and that in the previous experiments it must have been simply decomposed by the action of a ferment which quickly develops in urine containing biliary colouring matter. Five days later the patient discharged urine which, after precipitation with lead-salts, evaporated and extracted, yielded as much hippuric acid as healthy urine. Two further experiments upon the same patient yielded the same results. The patient recovered his health several weeks after the inquiry instituted upon him. Schultzen also examined the urine from a case of fresh icterus, from sup-posed catarrh of the common duct. It yielded hippuric acid, and in larger quantity after benzoic acid had been administered. Most remarkable was the case of an aged female, afflicted with closure of the common duct by a gall-stone. She had severe colic, was greatly jaundiced, and her feces contained no pigment. Hippuric acid was found in the urine, but only when it was mixed with the lead-salt immediately after emission. If allowed

to stand by itself for one-quarter of an hour after emission, it became decomposed, and then yielded no longer hippuric but only benzoic acid to analysis.

This experience, made upon pathological specimens and cases, furnishes evidence in support of the opinion which I have advanced in the physiological consideration of the origin of hippuric acid. The glykokoll of the glykocholic acid is probably not essential for the formation of hippuric acid in urine. The decomposition of hippuric acid in urine and the consequent appearance of benzoic acid may be due to the influence of ferments, or bodies capable of quickly generating ferments excreted with the urine by the deranged economy of the body.

One feature is very striking, both in these experiments of Schultzen and the observations of Erdmann. They always found either hippuric or benzoic acid, never a mixture of the two. In my own analysis a little benzoic acid was found, and had evidently been derived from three or four specimens only out of the twenty examined. But it was mixed with an overwhelming amount of hippuric acid. From this I conclude that fermentation once begun in the urine is quickly completed, as far as hippuric acid is concerned. But I also conclude that the benzoic acid in my own specimens was not due to fermentation, but present in each as a normal ingredient.

I examined the urine in a case of chronic anæmia for hippuric acid. On the first day of examination the quantity of urine amounted to 600 c.c., and contained 0.406 gm. of hippuric acid, also 25.2 gm. of urea, and 8.1 grains of uric acid. On the second day the patient, in addition to her diminished blood and vital powers, had a bad cold; 1500 c.c. of urine, containing 0.258 gm. of hippuric acid and 27 gm. of urea, were excreted. Only two little crystals of uric acid could be obtained from 400 c.c. of this urine by the addition of hydrochloric acid. On the third day of observation the amount of urine was 965 c.c., and contained 0.244 gm. of hippuric acid. On the fourth day the urine was 600 c.c.; urea, 21.6, gm.; hippuric acid, 0.316 gm. Peculiar in these four specimens was the very dark brown colour of the extract. The urine of the healthy man yielded a light yellowish-brown extract, which was only dark brown on the days when some benzoic acid was obtained besides the hippuric. In the case of anæmia, however, no benzoic acid was obtained on any occasion.

Spontaneous Deposits of Hippuric Acid from Human Urine.

As the type of hippuric acid deposits, we may consider the crystals which form after evaporation in urine containing the acid in solution. They are the long needle-like rhombic prisms in a variety of combinations, the crystals forming in groups of

stellar arrangement. The characters which distinguish the hippuric acid deposit at first sight from the uric, are the small amount of colouring matter it contains, the needle-like shape, and the stellar arrangement. The hippuric acid crystals have a tendency to become club-shaped at their ends. This tendency eventually results in the apposition of many acicular crystals to the end or both ends of a single prism.

Deposits of hippuric acid are by no means common. I have seen only very few instances of this kind, and in one benzoic acid had been administered as a medicine. On one occasion I found a deposit of this kind in the urine which had been passed by a young married lady after a severe attack of colic probably from gall-stones. Vogel has observed several times needle-like crystals of hippuric acid deposited upon larger crystals of uric acid. Ordinarily the proportion between the size of the crystals of this acid is reversed in favour of the hippuric acid crystals. Small needles of hypoxanthine may be fixed upon uric acid crystals. The diagnosis is ensured by filtering off the deposit, and extracting any hippuric acid by boiling alcohol. On evaporation of the solution in a watch-glass the acid will recrystallise.

The deposits of hippuric acid are by no means due to the same individual causes as those of uric acid, though the same causes may co-operate to produce such deposits; for hippuric acid being more soluble in water, it follows that the acid must be present in excess before any deposit can take place. This is known to be not requisite for a deposit of uric acid. Any sediment of hippuric acid can therefore only have been produced by the co-operation of two immediate causes: (1) a strong acid present in the urine to keep hippuric acid in the free state; (2) an excess of hippuric acid over the normal quantity, and exceeding the amount which the urine at a certain temperature can hold in solution.

CHAPTER XI.

INDIGOGEN. URRHODINOGEN.

INTRODUCTION AND LITERATURE.

THE urine of man and animals contains, if not regularly, at least very frequently, a substance which by certain chemical reagents, or by putrefaction, is so altered as to yield *indigo blue*. This substance in the pure state seems to be nearly, if not quite, colourless; but owing to the difficulty of obtaining it in an isolated state, of separating it from the normal yellow colouring matter of the urine, *urochrome*; from another yellow colouring matter, which easily passes into red, *urochrome*; from a third, perhaps not quite colourless, though but faintly coloured matter, which by decomposition with acids yields a red product, *urrohodine*, and which I therefore term *urrohodinogen*,—this indigogenous substance has always been ranged amongst the *colouring* matters of urine. This confusion has been carried to such a climax by some authors that they maintained that the yellow colour of the urine in health was solely due to the presence of this indigo-bearing substance, and by others to this, that while they allowed the normal colouring matter to be peculiar, they ascribed the yellow colour of the urine in many diseases to the prevalence of this supposedly yellow indigo-bearing substance. These opinions, which never had any foundation in fact, have been reiterated with blind pertinacity by ill-informed writers, so that it has become necessary to refute the errors one by one, and assert or reassert in detail the true teaching of science on these subjects.

That the indigo-bearing substance of urine is *colourless* follows from a variety of facts, such as that the most colourless urine, *e.g.*, the first urine in the reaction from cholera, and which frequently contains hardly any *urochrome*, yields the largest amount of indigo, and consequently contains the largest amount of indigogen that urine ever does contain. Further, the indigogen is best isolated from urine, in which it may be contained by processes which, as a preliminary, do endeavour to remove every trace of coloured ingredient from the urine, before applying the reagents for the precipitation of the indigogen.

Almost the same statement may be made with regard to the substance which by decomposition with acids yields *urrrhodine*. This *urrrhodinogen* also is present in the colourless urine of cholera reaction, and makes its appearance only by the aid of strong chemolytic and oxydising agents, and of heat. Indeed, so similar is the behaviour of indigogen and *urrrhodinogen* in this respect, and they seem to go so much together, that most authors have assumed them to be one body only, which by chemolysis yielded indigo and *urrrhodine* in atomic proportions. This assumption was propped up by a fallacy, namely, that *urrrhodine* was a kind of chemical twin-brother of indigo blue, its isomer, indigo red or indirubine. But *urrrhodine* cannot be the isomer of indigo blue, because it contains no nitrogen, and for the same reason cannot be identical with indigo red, whatever be the nature of this little examined substance.

In looking at the literature of this subject a little more in detail, we find that perhaps the earliest record of the occurrence in urine of a blue colouring matter is that by Janus Plancus ("Commentarii Instituti Bononiensis," ad ann. 1767). The first chemical description of a blue or violet colouring matter occurring in urine was given by Braconnot ("Ann. Chim. et Phys." 29, 252), who termed it cyanourine; and though he found that it had some similarity to indigo, believed it to be a separate organic base. Subsequently to this author several cases were recorded, in which a substance corresponding in character to cyanourine was discovered in urine. The first reliable observation, however, of the occurrence of indigo in urine is by Prout ("Stomach and Urinary Diseases," 3d ed., p. 96). The same substance afterwards also occurred to other observers.

Heller ("Archiv. für Chemie and Microsc." 1845) was the first to extract from urine a yellow substance, uroxanthine, which, by treatment with acids at a higher temperature, yielded him a blue substance, uroglaucline, and a red pigment, *urrrhodine*. The cyanourine of Braconnot he declared to have been a mixture of these two bodies produced by him. Kletzinsky (Heller's "Archiv." 6, 414) showed the identity of uroglaucline with indigo blue in a conclusive manner, and asserted, erroneously as we shall see, the identity of *urrrhodine* with indigo red. The observations of Heller were ignored, doubted, or misrepresented by many authors without practical experience. Virchow, however (Virchow's "Archiv." 6, 259) confirmed the observations of Heller, but more by microscopical than chemical criteria. He obtained the blue matter from every concentrated urine, and observed that when much indigo-producing substance was present the urine gave the copper test for sugar. Schunck ("Phil. Mag." (4) 14, (1857) 288) again isolated Heller's uroxanthine, and identified it with indican, which he had before discovered to

be the chromogen contained in indigoferous plants, and which, under the influence of acids or ferments, yields indigo blue, a peculiar kind of sugar, and a small quantity of other products. Schunck found his supposed indican in almost every specimen of human urine, and in the urine of many animals. In 1864 I (Hastings Prize Essay on "Urochrome," &c.) controverted this opinion of the glucoside nature of the indigogenous substance in urine, particularly on the ground that no sugar was formed in its chemolysis. This fact, now admitted and published as a novelty by Baumann (Pflüger's "Archiv." 13 (1876), 307), though evidently fatal to the indican hypothesis, remained, however, unheeded by numerous authors, who filled lengthy papers with records of test-tube experiments, destitute alike of value and of meaning, and not in a single instance even isolated, never analysed for its elementary composition any of the substances with which they dealt as if they were known quantities. Up to 1872 the test for the presence of the indigo-forming substance in urine had been hydrochloric acid or nitric acid, applied in a concentrated state, and in considerable quantity, assisted by heat up to boiling. But about that time one of the most assiduous adherents of the indican doctrine, Jaffé, found that the oxydising action of air in the presence of hydrochloric acid, or that of nitric acid, could also be supplied by hydrochloric acid, to which a minute trace of calcic hypochlorite, in the shape of solution of bleaching powder, was added. The blue colour then appeared immediately in the fluid, yet warm from the admixture of a volume of hydrochloric acid equal to that of the urine employed. The reaction was made the basis of a method of quantitative determination of indican, which yielded data, varying between the "unweighable" and the "colossal." About this time the discussion also began to gain in physiological interest by the observation of Kühne (Virchow's "Archiv. f. Pathol., Anat." vol. 39), that during the artificial fermentation of albumen in the presence of minced pancreas the indol of Baeyer was found. This was soon confirmed by others, and as after injection into the stomach, or injection into the circulation, of indol, the indigogenous substance appeared in the urine in apparently increased quantity, Jaffé formularised the new knowledge to this effect, that the albumen during the pancreas digestion furnished indol, which in the circulation was oxydised to indigo blue, then combined with sugar, and ultimately excreted as the glucoside indican. The "indigo red" found no place in this theory. Baumann now not only controverted the glucoside hypothesis of indican, but showed that the chromogen from *isatis indigofera* was different from that of (equine?) urine, and propounded that the latter, for which, notwithstanding that it was a body of a new type and not a glucoside, he still retained the name of indican, was a compound

acid, in which the radical of indigo blue and the radical of a body which we easily recognise as urrhodine were in firm union with the radical of sulphuric acid. However, urrhodine, or Baumann's red body, has not yet got a place in the pancreatic peptone hypothesis; and the sulpho-acid hypothesis was not proved by direct fact, but was only the result of an inference drawn from the determination of the precipitable and unprecipitable sulphuric acid contained in the urine of a dog, to which artificially prepared indol was given with the food in such quantities that the animal suffered from suppression of urine for thirty hours, and then discharged an albuminous liquid containing much of an indigo-yielding substance. By such high-pressure experiments is it now-a-days attempted to solve delicate physiological problems.

Modes of Isolating the Indigo and Urrhodine-producing Substances from Urine.

The attempts made in this direction have hitherto succeeded only very partially, and what has been obtained may with propriety be called concentrated impure solutions of the substances sought for. The processes to be described must therefore be considered as essential preliminaries to further discovery.

1. *Heller's Mode of Obtaining the Chromogens and their Products from Human Urine.*—The urine was precipitated by acetate of lead, and the filtrate evaporated to dryness at a low temperature. It was then extracted with ether, which, after distillation, left the chromogens as a yellow residue (Heller's uroxanthine).

Special attention must be directed to the fact, that by the precipitation with plumbic acetate, most of the normal urinary colouring matter, urochrome, was removed from the urine before it was prepared by evaporation for the extraction of the chromogens. In Schunck's proceeding, to be described lower down, this removal of the coloured ingredients was carried still farther. The precipitates by neutral and basic lead acetate in succession, or that obtained by basic lead acetate only, without previous application of the neutral acetate, contain none of the indigogenous, and only little of the urrhodinogenous substance, but contain much urochrome, and much of another yellow colouring matter, uroluteine, which easily decomposes in acid solution, and then shows before the spectroscope an absorption band at the meeting of green and blue.

Heller obtained the indigo blue and urrhodine from urine in the following manner:—The fresh urine is precipitated by a hot solution of acetate of lead, the filtrate is quickly freed from lead by hydrothion, and the excess of the latter is removed from the filtrate by boiling. This hot fluid is now poured in small portions, under constant stirring, into an equal volume of highly-

concentrated, fuming, pure hydrochloric acid. The fluid becomes indigo blue, bluish-green, and very dark. If the mixture becomes only violet or red, no deposit of indigo will be obtained. But if it becomes blue, and is allowed to stand for some time, a copper-red, shining, metal-like, dark blue crystalline pellicle appears. The fluid, after twelve hours' standing, is diluted with an equal portion of cold water, shaken, and put aside for twenty-four hours. A deposit, frequently inches high, settles towards the bottom; it is separated from the fluid by filtration, washed with boiling water until the washings have a neutral reaction, then washed with some dilute spirit of wine; lastly, it is dried in the water-stove, and over sulphuric acid.

The dry filter is now washed with ether so long as a red-coloured filtrate is obtained; the ethereal filtrates, which have an acid reaction, and a deep red colour, leave on distillation an uncrystallisable brownish-red resin, *urrhodine*. If the last portion of ether has left the filter quite uncoloured, the substance on the filter is quite free from urrhodine, and is now dried. All that part of the paper which shows no blue deposit is now cut off; the rest is cut into small pieces, put into a flask, and boiled strongly with alcohol of 0.83 to 0.9 specific gravity. The alcohol is poured off as often as it assumes a sky-blue or pale blue colour, and the residue is extracted with a new portion of boiling alcohol, until, on protracted strong boiling, the alcohol remains colourless. The alcoholic extracts are filtered while boiling hot, concentrated to a convenient bulk, and put aside in a well-closed bottle. After the fluid has become cool, in some cases after protracted standing, *indigo blue* is precipitated in microscopical masses of imperfect crystals. The supernatant alcohol becomes quite colourless.

2. *Schunck's Modes of Obtaining the Chromogens and their Products from Human Urine.*—*a.* The urine is mixed with plumbic acetate as long as this produces a precipitate, and the latter is removed by filtration. Basic acetate of lead is now added to the liquid until the precipitation is complete, and the deposit again removed by filtration. The liquid is now almost colourless, as nearly the entire amount of the yellow colouring matters of urine, together with all the phosphoric and sulphuric and much hydrochloric acid, and a few other ingredients have been removed in combination with the lead precipitates. On addition of ammonia to this nearly colourless liquid, an almost white precipitate is obtained, the quantity of which is much less than that of either of the other two precipitates. If this precipitate is decomposed by an acid and the mixture filtered, the filtrate deposits indigo blue on standing.

b. The following proceeding dispenses with the first precipitation and filtration. The urine having been mixed with basic

acetate of lead until no more precipitate is produced, is filtered, and after the precipitate has been washed with water, the liquid is mixed with an excess of ammonia, which always produces more or less of a white or yellowish-white precipitate. This precipitate is collected on a filter, slightly washed with water, and then treated with dilute sulphuric or muriatic acid in the cold. After the whole of the oxide of lead has combined with the acid employed, the liquid is filtered. When there is much of the indigo-producing body present, the filter acquires a blue tinge, small particles of blue pigment are seen dotting the surface of the sulphate or chloride of lead, and the surface of the liquid, which is of a brownish-purple colour, in a very short time becomes covered with a thin pellicle, which is blue by transmitted, and copper-coloured by reflected light; particles of the same blue substance being at the same time found attached to the sides of the vessel. When there is less of the indigo-producing body present, this pellicle only appears after some time, sometimes not until the next day. After twenty-four hours, however, the action of the acids is always completed, so that if no indigo blue then appears, or can be detected on examination of the deposit, the total absence of the indigo-producing body may be inferred. The deposited matter collected on the filter, after being washed, is treated with caustic soda, which dissolves a portion, acquiring thereby a brown colour. The portion which remains undissolved, after being again collected on a filter and washed, is treated with boiling alcohol. In most cases, the alcohol thereby acquires a bright blue colour. When, however, the quantity of deposit formed is tolerably large, the boiling alcohol first dissolves another substance, which imparts to it a fine purple colour. That which the boiling alcohol leaves undissolved is a bright blue powder, having the properties of indigo blue.

From this description it is clear that the liquid obtained by decomposing the last lead precipitate with acid, deposits, under the influence of the excess of free acid, and probably of the oxygen of the air, at least three matters, one soluble in (very dilute) caustic soda, probably *uromelanine*; another easily soluble in alcohol, erroneously supposed to be indigo red, being *urrhodine*, and yielding by admixture with the first portion of blue indigo solution a purple solution, and ultimately *indigo*, which is indeed mostly only partially dissolved by the boiling alcohol; another part remaining insoluble, and in Heller's experiment attached to the paper.

When the acid liquid from which the three coloured bodies described in the foregoing have been obtained by standing at the ordinary temperature during twenty-four hours is boiled, it deposits a dark brown powder, which contains no indigo, and is

mainly a mixture of the decomposition products of urochrome, described under the chapter referring to that body.

3. Both indigo and urrhodine can be obtained from urine, which contains their generators, by mixing the filtered liquid with an equal volume of concentrated pure hydrochloric acid, and allowing the mixture to repose for three days. At the conclusion of that time the reaction is completed, and the product, an apparently voluminous brownish-red flaky mass, is collected on a filter and washed with water until free from hydrochloric acid. The matter on the filter is now washed with cold alcohol, which removes the urrhodine, next with hot alcohol, which extracts some urrhodine and some indigo blue, which together form a violet solution (yielding indigo and faint urrhodine spectrum), and leaving perhaps a trace of blue indigo on the paper, of which a portion, but rarely the whole, may be extracted by boiling the paper with alcohol. If the operation has been carefully conducted, no matter soluble in caustic soda or ammonia with a brown colour (uromelanine) is obtained. It must be observed that in this process some urrhodine is always obtained, whereas, not rarely, indigo is not obtained. This seems to point to the conclusion that indigo and urrhodine do not derive from one and the same body, but from two different generating substances, and that whereas urrhodinogen seems a constant, indigogen is not a constant but only a frequently occurring ingredient of urine.

4. Baumann's process of isolating the indigogen seems to have been carried out on the urine of horses. When he tried the so-called method of Hoppe-Seyler, which is in the main the proceeding by which Schunck obtained his indican from indigoferous plants, he always obtained pyrocatechin. But when he dissolved the lead precipitate containing the indigogen in alcohol, and treated it in stages with ether, some of the precipitated fractions were obtained free from pyrocatechin, but contained indigogen. This formed very stable salt-like compounds with metals, particularly alkalies, and could not be separated from them by acetic or hippuric, but easily by oxalic acid and the strong mineral acids. The indigogen in the free state was very unstable.

Baumann's process for obtaining, as he termed it, relatively pure solutions of indigogen is the following:—The urine is evaporated to a syrup and extracted with alcohol; the alcoholic extract is again evaporated to a syrup; this is strongly acidified with sulphuric acid and extracted with ether, containing one-tenth of alcohol. The ether solution is decanted into a separating funnel, and at once mixed with a little water, so that after strong shaking a lower watery layer separates from the ether. This water now contains the indigogen. It is isolated and immediately neutralised with potassic carbonate, and the solution evaporated to dryness. The residue is extracted with absolute alcohol, which

leaves phenyl-sulphate of potassium undissolved. The alcoholic solution is now mixed with an equal volume of ether, whereby the potassium compound of indigogen is precipitated as a syrup. By repeatedly dissolving this syrup in alcohol, and reprecipitating with ether, the urea can be entirely removed. At last a yellow-coloured syrupy liquid is obtained, which can be dried at 100° without undergoing decomposition. It seems, however, that this salt yet contained some hippuric acid, from which it has to be freed by transformation into calcium salt, and treatment with absolute alcohol. At this point Baumann's description of chemical proceedings diverts to experiments with indol upon a dog, by means of which he endeavours to make probable what he fails to prove by direct evidence, namely, that his indigogen is a sulphuric acid compound. For the purpose of testing the hypothesis of the glucoside nature of indican, he heated some of the yet impure indigogen with dilute sulphuric acid on the water-bath, neutralised with calcic carbonate, evaporated the mixture to dryness, and extracted the residue with warm alcohol. This solution was again evaporated, and the residue extracted with water. A red resin, soluble with red colour in ether and alcohol, and sublimating in prisms, was left undissolved. The yellowish watery solution was decolorised with animal charcoal and concentrated; it had no effect on polarised light, and did not reduce alkaline copper solution. No pure or crystallised substance was obtained in the above proceeding, and not a single product was analysed.

Physical and Chemical Properties of Indigo Blue from Urine,
 C_8H_5NO .

It assumes the shape of minute irregular crystals when slowly precipitated from its solution, or when obtained by sublimation. Its vapour is of a violet-red colour.

When freshly precipitated from its solution in caustic alkali and glucose, or when newly sublimated, it is somewhat soluble in boiling alcohol. The sky-blue solution retains the indigo for less than twenty-four hours, after which it is found entirely deposited, and cannot be again dissolved in the same alcohol by heat. The solution before the spectroscope shows an absorption band in yellow overlying the D line, and the blue part very clear. When the blue part is not clear, but obscured, the indigo is not yet quite pure, but contains yet some urrhodine.

It dissolves on trituration in fuming sulphuric acid, forming a dark blue solution, which on immediate dilution with water deposits traces of a purple substance. The blue solution dyes sheep's wool of the same colour, and the latter yields its colour to boiling sesquicarbonate of ammonia. The blue acid solution, like the alcoholic solution of the free indigo, exhibits an absorption band overlying the yellow in the spectrum. Warmed with

an alcoholic solution of potash it forms a green solution, which when heated to boiling becomes red. On cooling it becomes green again, and red again on a second boiling; this change can be several times repeated before the solution loses the faculty of producing it.

Digested in a closed bottle either with grape-sugar and potash, or with orpiment, water, and excess of alkali, it yields a solution which is not blue, but which on admission of air deposits indigo at the top and gradually downwards, or becomes suddenly blue on being shaken with air. Parallel to this is the reduction of indigo in the urine in which it has been formed by putrefaction. When the bottle containing it is stoppered the indigo dissolves; but when the air is again admitted, and the liquid shaken with it, the indigo is again deposited, and collects as a copper-coloured scum on the surface. The alcoholic solution and the solution of the sulpho-acids are both made colourless by nascent hydrogen, or other reducing agents, *e.g.*, zinc and hydrochloric acid, hyposulphites, or alkaline solution of tin protoxyde.

These reactions prove incontestably that the blue pigment from urine is identical with indigo blue from plants.

The Chromogen of Indigoferous Plants, Indican.

The chromogen of indigoferous plants is a peculiar colourless substance, which has been obtained (from *Isatis tinctoria*, for example) by extraction with alcohol, precipitation of the extract by acetate of lead, and decomposition of the precipitate, first by carbonic acid, afterwards by hydrothion, when it remains in solution in the filtrate. On evaporation there is left a gum-like mass, indican, which, when boiled with acids, yields indigo blue, a peculiar description of sugar, and a small quantity of other matters. The same decomposition is brought about by fermentation. The chromogen is soluble in water, alcohol, and ether. Schunck, who first observed this substance and asserted its identity with the chromogen of urine, also stated that the solution of the vegetal could be evaporated without change, while that of the animal principle was destroyed by heat.

Baumann tested some extract of leaves of *Isatis tinctoria*, and found that with hydrochloric acid, containing in 100 c.c. one to two drops of a solution of one part of chloride of lime in twenty parts of water, it produced indigo immediately, which could be taken up by ether. The isatis extract could not be heated without decomposing immediately; the solution, even when made alkaline with sodic carbonate, lost all chromogen in less than an hour. Animal indigogen, on the other hand, could, according to him, be boiled with caustic potash without decomposing. Baumann failed in the attempt to isolate any of the vegetal chromogen from fresh isatis plants. It is therefore evident that

the physiology of animal indigogen can derive no help from these experiments of Schunck and Baumann, and that the *vegetal indican* is a substance with which the *animal indigogen* must not be confounded.

The following paragraphs are given to enable the student to readily procure himself materials for study and comparison.

Mode of Obtaining Indigo Blue and Indigo Red from the Indigo of Commerce.—When the indigo of commerce is boiled with dilute acetic acid, *indigo glue* goes into solution, and may be obtained from it by evaporation, as a yellowish, varnish-like mass, which is soluble in water and alcohol. The substance thus freed of indigo glue is next treated with solution of caustic potash, which dissolves *indigo brown*. This latter substance may be precipitated from the solution in potash, by the addition of sulphuric acid, in the shape of a voluminous brown mass, which possesses an acid reaction. Indigo thus treated with acid and alkali yields to boiling alcohol a red colouring matter, *indigo red* (indirubine of Schunck), which on evaporation of the alcohol remains in the form of a reddish-brown powder, soluble, with a dark red colour, in alcohol and ether. On heat being applied to it, it is partly sublimated without decomposition; another part is decomposed, and yields a sublimate of colourless crystals. After the extraction of indigo red there remains *indigo blue*, which constitutes the greater bulk of the substance originally employed. This indigo blue may be further purified in the following manner:—

Crystalline Indigo Blue by Sublimation.—Roughly powdered indigo is placed in a shallow porcelain dish, or on a bright plate of silver or platinum, and heated cautiously. On the surface of the fragments there are formed reticular masses of crystals, consisting of pure indigo blue. When heated in a glass tube indigo evolves purple fumes, which suddenly condense, and settle on the surface of the powder from which they were evolved. It is, however, impossible to conduct the sublimation so as not to destroy a part of the indigo by overheating.

Crystalline Indigo Blue by Reduction.—On mixing powdered indigo with grape-sugar, spirit of wine, and concentrated solution of caustic soda, and immediately closing the bottle and letting stand for some time, a yellow solution of indigo white, hydrogenated indigo (C_8H_6NO), in the alkali, results. If the clear fluid is now decanted and exposed to the air, the reduced indigo again becomes indigo blue, which is slowly deposited in a crystalline form.

Amorphous Indigo Blue by Reduction.—If common indigo is mixed with caustic lime and a solution of sulphate of suboxyde of iron, and, the air being excluded, is allowed to stand for some time, the suboxyde of iron transforms indigo blue into indigo

white, which latter is soluble in lime. When the clear yellow solution is poured into dilute hydrochloric acid, and the mixture is exposed to the air, the indigo white rapidly absorbs oxygen, and is precipitated in the form of indigo blue.

Physical and Chemical Properties.—The crystalline indigo blue forms purple, scaly crystals. The amorphous modification possesses a blue colour with a purple hue, and by friction becomes of a glistening copper-red colour. In the form of a subtle powder it is blue. It has neither taste nor flavour, and is insoluble in water, ether, and dilute acids and alkalies. Its solubility in alcohol only lasts for a few hours after its formation, and then is entirely lost.

Isatine.—The oxydation of indigo blue yields in the first instance *isatine*, $C_8H_5NO_2$; this, under the continued influence of oxydising agents such as nitric acid, is transformed into nitrosalicylic, lastly into picric acid. The compounds obtained from *isatine* by substitution are very numerous. Under the influence of ammonia it forms a series of remarkable amides. When introduced into the alimentary canal of animals or below their skin it gives rise to colour-producing substances, which have, however, nothing in common with the natural chromogens or colouring matters (R. Niggeler, "Arch. Experim. Path. and Pharm." 3, 167).

Indol.—Indigo is extracted with alcohol, and then boiled with tin and hydrochloric acid until it is transformed into a brownish-yellow powder. This is now washed and distilled with a large excess of zinc dust from a copper retort. The distillate, a thick oil, is treated with dilute hydrochloric acid to remove aniline, and then distilled with superheated steam, and the distillate placed over sulphuric acid. Colourless hard crusts of crystals of *indol* are deposited, which are recrystallised from water. Indol crystallises in scales resembling benzoic acid, fuses at 52° , sets again in a crystalline form on cooling, is easily volatile, but cannot be distilled by itself without change. It is easily soluble in alcohol, ether, and hydrocarbons. Traces of ether vapour cause it to deliquesce. It has a peculiar odour, reminding of naphthylamine. It is a feeble base, and has the composition represented by the formula C_8H_7N (Baeyer). According to Nencki indol obtained from albumen shows vapour density, determined at 218° in an atmosphere of naphthaline vapour, of between 4.33 and 4.62, air as unit, while the formula C_8H_7N requires 4.05.

When the watery solution of indol is mixed with a dilute solution of fuming nitric acid in water, a voluminous red precipitate of needles of probably nitrite of indol ensues; this on boiling with water or alkalies yields again indol. In alcohol this body undergoes decomposition. Indol in alcohol, when treated with nitrous acid, yields red needles of another compound.

The alcoholic solution of indol imparts a cherry red colour to a chip of fir-wood, but the colour after some time passes into a dirty brown-red.

Urrhodine.

This body is always obtained by the processes for obtaining indigo blue above described, even in cases when no indigo blue is obtained. This seems at first sight to indicate that it has not the same origin as the indigo; and until the contrary is proved, it will be best to adhere to the hypothesis that it is the product of the decomposition by hydrochloric acid of a substance at present not isolated, *urrhodinogen*. Urrhodine is frequently stated to be identical with the indigo red or indirubine extracted by alcohol from commercial indigo; this indigo red is further maintained to have the same composition as indigo blue, and to be in fact its isomer. Whatever may be the relation of indigo red to indigo blue, urrhodine is not an isomer of indigo blue, and is not similar to it in composition, as it contains no nitrogen.

Urrhodine is soluble in ether with a truly red colour. The solution must be freed from every trace of hydrochloric acid by long continued washing with water. Its spectral phenomena are very characteristic. A concentrated solution cuts off all light except red. After considerable dilution with ether until the solution has a light red colour, the blue of the spectrum appears, but the whole of the green remains extinguished by a characteristic absorption band of about 2 degrees of intensity, black being ten degrees.

The red resinous mass of urrhodine left after evaporation of the ether was subjected to elementary analysis by the process of combustion *in vacuo* (see Thudichum and Kingzett, "Journ. Chem. Soc." 1876, ii., 363), with the following result: (1) 0.0178 gm. urrhodine gave 26.16 c.c. of normal gas, of this only 0.16 c.c. were not absorbed by caustic potash, and consequently nitrogen. The calculated carbon from 26.00 c.c. CO_2 is 78.3 per cent. (2). 0.0184 gm. gave total normal gas 28.0 c.c. of which 0.2 c.c. were nitrogen; the carbon calculated from 27.8 c.c. CO_2 is 81.0 per cent. Now, although the difference in the quantity of carbon found prevents us from accepting either quantity as absolutely correct (these analyses were made before we had found the means of correcting irregularities described in the paper just quoted), we are fully justified in the following conclusions:—Urrhodine contains about 80 per cent. of carbon. *It contains no nitrogen. It is consequently not identical with indigo red, and is not an isomer of indigo blue, but an animal substance of its own kind.*

Urrhodine therefore contains several per cent. more carbon

than phenol. Some of the ethereal solution dropped into mercuric nitrate produces a slight turbidity, the resin separating and floating on the top of the liquid without producing any red coloration or precipitate. Nitrate of silver solution is coloured of a faintly rosy hue on boiling, but no reduction is produced. These reactions exclude the presence with urrhodine of phenol and cresol. It is, however, not asserted that the urrhodine obtained as above is a pure substance. It shows signs of crystallisation in its amorphous substance. When subjected to sublimation it yields a red vapour, which condenses, and the sublimate then clearly consists of two substances, one being an amorphous red matter, the other colourless scaly crystals. The red matter remains soluble in spirit, but the crystals seem little soluble in it.

Physiological Relations of the Indigogen of Urine.—Kühne made the observation, that fibrin while being digested with pancreas at 40° to 45° evolved a strong odour of naphtylamine or indol. A continuation of the experiment showed that this phenomenon was not due to pancreatic digestion proper, inasmuch as the pure ferment pancreatine did not yield any of the strong smelling substance when digested with albuminous substances. When Kühne ("Berlin Chem. Ges." 8, 206) distilled dry albumen with eight to ten times its weight of caustic potash in metal retorts, at temperatures rising gradually and slowly to a dull red heat, redistilled the residue with water, and then extracted it with ether, he obtained in the united distillates and extracts a body which had many of the properties of indol, though it was not identical with it. The body is supposed to be identical with that described by Bopp, as obtained during the fusion of caseine with potash, having a smell of fæces. Nencki and Frankiewicz ("Berlin Chem. Ges." 8, 336) now enlarged the experience of Kühne by the following experiment:—300 grm. commercial serum-albumen are dissolved in 4½ litres of water, and mixed with from 300 to 400 grm. of minced pancreas of the ox. The whole is kept at a temperature of from 40° to 50° during from 60 to 70 hours. After cooling the mixture is filtered, acidified with acetic acid, and distilled to about one quarter of its original volume. The somewhat turbid distillate after filtration is perfectly clear. It is now made alkaline by milk of lime, and shaken with an equal volume of ether. The ethereal solution after distillation leaves a reddish oil, which smells of indol. Mixed with a little water, the oil, after some time becomes crystalline, and after being recrystallised from hot water, appears as pure indol with the properties above described.

Albumen from eggs yields the same result as serum-albumen; but the experiment with gelatine yields so little, that the trace obtained is supposed to be derived from the albumen of the pancreas and not from the gelatine.

From these experiments it follows that the albuminous substances under the influence of a kind of putrefaction in the presence of pancreas and much water, continued during nearly thrice twenty-four hours, are capable of yielding indol. From the experiments of Jaffé it further follows, with some probability, that indol, when introduced into the organism reappears in the urine transformed into a substance, which by hydrochloric acid and a little hypochlorite of lime yields indigo blue, like the natural indigogenous substance. It cannot be said that the identity of the indigogenous matter which appears after the ingestion of indol with the natural one is at present a matter of certainty. But that the natural indigogen of the urine *may* be derived from the albumen of the food will probably be allowed. Now, if *pure pancreas digestion*, that is to say, digestion of albuminous matters in alkaline solution, with the aid of pure pancreatic ferment, does not yield indol, then the indigogen of the urine cannot have its origin in normal pancreatic digestion. But as indol is obtained from a process half putrefactive, half digestive, such as not rarely takes place in overloaded or weak intestines, it is not impossible that the indigogen of urine is frequently or mostly a product of such a process. In the intestine of a perfectly healthy human being little or no indol is probably produced, and consequently little or no indigogen appears in his urine. But in others, particularly the weak and chronically sick, or those recovering quickly from severe diseases, such as cholera, or in those who have swallowed more food than the digestive powers are capable of disposing of in an absolutely normal manner, the digestion of the albuminous matters is not completely normal, but participates of the nature of putrefaction; and under these circumstances some indol is formed, and appears as indigogen in the urine. This pointed hypothesis seems to arise easily out of the preceding facts. But it need not be the only explanation of which the appearance of indigogen in the urine is capable. In omnivorous or herbivorous animals the indigogen of urine may, and in horses, in the urine of which it is said to occur more copiously than in any other, probably does, owe its origin not only to the decomposition of a portion of the under-digested albuminous matter, but also to the introduction into the intestine of vegetable principles, which, like the indican of *isatis*, is soluble, fermentable, and easily furnishes a radical for the formation of the indigogen which appears in the secretion. With these data the fact is certainly in harmony, that indigogen is not invariably present in the urine of all individuals; that there are individuals in whose urine it is as a rule not found; that there are others in the urine of whom it is found, or not found, at intervals, changing in a manner which by the observers has been termed

capricious; and that there are persons from whose urine it is never absent.

Quantities of Indigogen Secreted.

The physiological quantity of the chromogen in urine must be exceedingly small. By working for several weeks on the urine of two individuals, which contained a comparatively large quantity of chromogen, Schunck obtained one grain of indigo blue.

The urines of forty different individuals, all of whom were apparently in a good state of health, yielded, with one exception only, more or less indigo blue, when examined in the manner described. These individuals belonged to both sexes, and they were of ages varying from seven to fifty-five. The majority were persons of the working classes. The largest quantity of indigo blue was obtained from the urine of a man above the age of fifty, a publican. The urine of a young man, aged thirty-two, a servant, yielded almost as large a quantity. Among the rest, the urine of a young man, aged twenty-five, an engraver; that of a clerk, aged twenty-three; and that of a girl, aged twelve, who had been a cripple from infancy, were alone remarkable for the amount of indigo blue which they yielded. In all these cases, the indigo blue was accompanied by the substance imparting to alcohol a purple colour, urrhodine. The other specimens afforded much less, sometimes mere traces. In all cases, however, in which the urine of the same individual was examined at different times, the amount of indigo blue obtained from it was found to vary exceedingly, it being sometimes considerable, and occasionally dwindling down to a mere trace. It was only very rarely, however, that none was found. In the case of the individual first referred to, the urine gave on one occasion not a trace, and this took place when he was engaged in performing labour, unusual for him both in its nature and amount. In Schunck's own case, as well as in that of his assistant, the amount varied most capriciously from a tolerable quantity to a mere trace, occasionally even none at all being obtained.

Several experiments with different kinds of diet, in order to ascertain the effect on the amount of indigo blue yielded by the urine, led to no very decisive results.

*Estimation of the Quantity of Indigogen contained in Urine,
according to Jaffé.*

From one litre to a litre and a half of urine is made alkaline with milk of lime, and the precipitation of the phosphates is completed by calcic chloride. The mixture is allowed to

stand during twelve hours, and the liquid is then, after filtration, evaporated, lastly on the water-bath to a thick syrup. During the evaporation the reaction of the liquid must be tested from time to time, and if it be acid a little sodic carbonate must be added. The syrupy residue is warmed up with half a litre of alcohol, and after complete mixing is allowed to stand for from twelve to twenty-four hours. The alcoholic solution is then filtered, and the alcohol distilled off. The residue is dissolved in a large quantity of water, and treated with a very dilute solution of ferric chloride, any large excess being avoided. The ferric precipitate is filtered off, the solution is mixed with ammonia, heated to boiling, filtered from the ferric precipitate, and evaporated to the bulk of about 200 c.c. This fluid represents the concentrated extract of the quantity of urine taken. From this solution the indigo is to be precipitated by an exactly appropriate quantity of chloride of lime solution. This is found as follows:—A measured quantity is diluted gradually with measured quantities of water until ten cubic centimetres of the dilute solution, when mixed with an equal bulk of strong, pure hydrochloric acid, and treated with one drop of a saturated solution of chloride of lime, yields just a perceptible blue colour. This is the standard unit of the reaction. It has been found empirically that the quantity of indigogen contained in these most dilute ten cubic centimetres of solution, when contained in more concentrated solutions, requires the quantity of hypochlorite of lime contained in half a drop of the saturated solution. Or, in other words, as many times as it has been necessary to dilute the concentrated indigogen solution with water, so many drops divided by two have we to add to each ten cubic centimetres of the original solution (mixed with its bulk of hydrochloric acid) in order to obtain all the indigo as a blue precipitate.

Supposing, therefore, that a litre of urine had yielded 200 c.c. of extract, and that of this a sample had required to be diluted with ten times its bulk of water, before, on repeated testing, 10 c.c. of it with 10 c.c. of HCl and one drop of saturated chloride of lime solution gave the required faintest blue reaction, then every 10 c.c. of the 200 c.c. of extract require, besides 10 c.c. of HCl, five drops of chloride of lime solution for complete decomposition of the indigogen. When the indigogen in any extract has thus been decomposed, the mixture must be allowed to stand for twelve hours. The precipitate is collected on a weighed filter of Swedish paper, which has previously been extracted with hydrochloric acid. It is washed with cold and hot water, and with dilute ammonia, and is then dried in the water-stove and weighed. By this proceeding Jaffé extracted from the urine of twenty-four hours, say, 1500 c.c. from 4.5 to 19.5 milligrammes of impure indigo. The urine of dogs yields relatively

more; that of cows much more; that of horses, on an average, twenty-five times as much indigo as human urine.

Variation of Indigogen under Pathological Conditions.

A small number of samples of urine from patients which Schunck had an opportunity of examining yielded, with one exception, no more indigo blue than the generality of healthy urines. Of two samples of urine from patients with albuminuria, one gave a small quantity of indigo blue, the other not a trace. Several specimens of diabetic urine yielded it, and one of them a much larger quantity than had been obtained from any other specimen of human urine. Heller found more of the indigogen in the urine from persons suffering from diseases of the serous membranes, the kidneys, and the spinal cord. Jaffé (*Centralbl. Med. W.* 1872, Nr. 1, Nr. 31, 32) finds that in the dog the quantity of indigo obtainable varies with the diet, so that animal diet yields the most, a diet poor in nitrogen the least indigogen. During starvation a trace of indigogen continues to be produced until death. Under certain pathological conditions the quantity of indigogen in urine is much increased. Thus in all cases which produce complete obstruction of the small intestine. In a case of ileus, which terminated fatally, very large quantities of indigogen appeared in the urine during the course of the disorder. In similar cases the increase is up to 10 and 15 times the normal quantity. Artificial obstruction of the small intestine in dogs by tying caused an increase in the quantity of indigogen, beginning on the second day, and lasting, in case the animal survived, until death. In a case of incarcerated hernia the amount of indigogen in the urine was increased during the incarceration.

In purulent peritonitis the indigogen excretion is also increased, probably from retardation of the action of the intestines.

Indigogen in the Urine of Cholera Reaction.

In apparent contrast to the data just stated, is the condition of the urine in certain cases of violent diarrhoea, but particularly in the reaction stage of Asiatic cholera. (see Thudichum "Report on Cholera Chemically Investigated," 9th Rep. Med. Off. Privy Council for 1866, p. 486. *et seq.*). The production of indigo from the urine of cholera patients was first observed by Gubler ("*Gaz. Med. de Paris*," Dec. 16, 1854). The urine which gave him the reaction was generally very pale. He found the blue more evident when nitric acid containing nitrous was used. These observations were a year later confirmed by H. Osborne ("*Med. Times and Gaz.*" March 1855, 307) and Lauder Lindsay (*ibid.*, May 1855, 460). Osborne observed that the urine of a cholera

patient recovering from collapse had a dark colour and a turbid appearance, was acid, and of sp. gr. 1020. The addition of a little pure nitric acid changed the colour to reddish, then deep violet, and a blue powder was ultimately deposited. When nitric acid containing nitrous was used, effervescence was produced, and a brown precipitate subsided, in which the microscope discovered specks of blue matter; the supernatant urine remained of a straw colour instead of a deep violet. Hydrochloric acid acted exactly like nitric in the production of the blue precipitate and violet coloration. The blue matter was soluble in alcohol. The urine of the patient gave a less amount of blue precipitate as convalescence became established. Lindsay's first case was that of a man, aged 52, recovering from collapse. The first urine which could be collected was passed on the morning of the third day; its sp. gr. was 1020; it was acid, slightly albuminous, and contained casts of the tubules, bladder-epithelium, dumb-bells, and granular and globular urate. Nitric and hydrochloric acid both produced the reaction, the urine being first heated, and the acid added to the boiling liquid. On standing, the tube became coated with a greenish-blue granular deposit. On the fourth day the urine gave no pigment reaction. Hassall, in his report to the General Board of Health on the chemical examination of the urine of cholera patients of the epidemic of 1854, gave an account of numerous instances in which the urine of cholera patients developed indigo by fermentation on standing, without the aid of reagents. Thus out of 29 samples of urine of one patient, 18 are said to have developed indigo. The blue colour of small particles, sometimes only visible with the aid of the microscope, was apparently the only criterion upon which they were assumed to be indigo. The reaction with nitric acid, which is exhibited by the earliest urine of cholera patients, was also observed by Buhl ("Official Report on Cholera in Bavaria," Munich, p. 521). He only obtained violet or purple, but no actually blue reaction, probably because he omitted to boil the mixture.

During the cholera epidemic of 1866 a number of specimens of first urine of cholera patients came under my observation which yielded the purple and blue reaction. The precipitates obtained by boiling the urine with appropriate quantities of nitric acid were mostly more or less coloured. Thus in one case the precipitate, which consisted mainly of albumen, was of dark brownish purple colour, and yielded to alcohol a purple-blue matter, which exhibited before the spectroscope the absorption band overlying the D line, but, unlike indigo, had the blue light entirely absorbed from the line C to the end. Similar precipitates yielding solutions offering the same spectral phenomena, were obtained from a number of cases. In other cases, however, a pink coloration was obtained with nitric acid, and the precipi-

tate gave a red solution with an absorption band, fainter, but in the same position as that of the blue solution. I carefully compared the spectra to those of different indigo solutions, and came to the conclusion, that however similar to indigo, they were not quite identical, and consequently I termed the blue matter *urocyanine* and the red one *urorubine*. All the observations which I then recorded are perfectly correct in every particular, but they require a somewhat different interpretation. I was not then aware of the effects which different solvents and slight admixtures and variations in temperature have upon the phenomena of absorption in the spectrum. These effects I only discovered during my studies of the luteine compounds (11th Rep. of the Med. Off. for 1868, pp. 190, 193).

The spectrum, then, of the blue and red matter from cholera is that of indigo as regards the absorption; the difference in width and intensity is caused by different concentrations and temperatures; the slight shifting of the bands depends upon the different concentration of the solvents employed, which in the case of the urinary matters were of necessity very dilute and somewhat acid. The urocyanine is really indigo, with a little urrhodine absorbing the blue; the urorubine is urrhodine containing a little indigo in solution, producing the specific absorption. Whether the blue was absorbed by urrhodine alone, or also by a product of its reaction with nitric acid, or by a third independent matter, remains to be decided. For this diagnosis the data of comparison, which were not then extant, are now at hand in the foregoing part of this chapter, and in other chapters of this treatise.

We can now give a not improbable explanation of the occurrence in unusually large quantities of indigogen in early urine passed by patients recovering from cholera collapse. In the course of the choleraic process large quantities of albuminous matters in the muscles and organs lose their colloid state; and having in this process of liquefaction absorbed the necessary amount of heat, and thus produced the low temperature observed in all cases of collapse, pass into the blood, and from this into the intestinal canal. Here they are immediately subjected to a fermentative process, which resembles in many respects the kind of putrefaction modified by pancreatic ferment which we have described above. Indol is no doubt produced, and the rose-pink colour, which intestinal contents and evacuation of cholera patients give with nitric acid (*see* p. 483 of my Report for 1867), and which has hitherto not been explained, is probably due to a reaction which indol in dilute solution is known to give with dilute nitric acid containing nitrous. Of this indol the greater part is discharged in the rice-water evacuation; but another part passes on the resumption of absorption from the

intestine into the blood, and is excreted as indigogen with the first urine. The first urine is favourable to the discovery of indigogen, as it contains little or no urochrome, which by treatment with acids might yield dark-coloured products, and thus obscure the indigo and urrhodine produced. That not all the indol formed in the intestine and absorbed into the blood reappears as indigogen in the urine is probable from an experiment by M. F. Masson ("Arch. Physiol. Norm. et Pathol." Paris, 1874), who found that after an injection of 0.135 gm. of indol, with 20 c.c. of water, under the skin of a rabbit, 0.0455 gm. of indigo were obtained from the urine, or only one-third of the quantity which should have been obtained if all indol had been transformed into and excreted as indigogen.

CHAPTER XII.

PYROCATECHIN, $C_6H_6O_3$.

HISTORY AND LITERATURE.

PYROCATECHIN was first observed in human urine by Müller and Ebstein (Virchow's "Archiv." 62, 554), next by Fleischer ("Berlin Klin. Wochenschr." 1875, Nr. 39 and 40) and Fürbringer ("Centralbl. Med. Wissench." 1875, p. 873). Boedecker's alcapton ("Ann. Chem." 117 (1861), 98) is probably identical with pyrocatechin. Baumann (Pflüger's "Archiv." 12 (1876), 63) showed that this body, though perhaps not a constant, is yet a very frequent ingredient of human urine, and is always present in the urine of horses. According to a later communication by Baumann (Pflüger's "Archiv." 13 (1876), 300), pyrocatechin occurs in the urine of horses, partly in the free state, partly in combination with sulphuric acid, as pyrocatechin-sulphuric acid.

Modes of Extracting from Human Urine.

From one to two litres of urine are acidified and evaporated; the residue is extracted with ether. The ether is distilled off, and the residue redissolved in water is tested for pyrocatechin by the reactions to be described.

Modes of Extracting from the Urine of Horses.

The urine is acidified with acetic acid and extracted with ether; the ether extracts are distilled, and the resinous black residue is dissolved in water and filtered, to the filtrate a few drops of lead acetate are added to effect a purification of colouring and resinous ingredients; the filtrate is cautiously neutralised with ammoniac carbonate, and then treated with lead acetate as long as a precipitate is produced. This is filtered, washed, and decomposed by hydrothion under water; the filtered solution is concentrated, and having a strongly acid reaction, becomes again coloured. It is therefore neutralised with barytic carbonate, and again extracted with ether. The ether is distilled off, and the residue taken up in water, filtered, and tested. In this manner Baumann obtained pyrocatechin in the crystallised state, but never pure enough for subjecting it to elementary analysis.

*Mode of Showing that Pyrocatechin is Present in Urine
(of Horses) in a Combined Form.*

200 c.c. of horse's urine are acidified with acetic acid and extracted with ether. The urine, which is now free from pyrocatechin, is heated on the water-bath for some time with hydrochloric acid, and when cool again extracted with ether. These extracts yield a reddish-brown resinous mass, from which water extracts hippuric and benzoic acid, phenol, pyrocatechin, and some resinous bodies. The residue is extracted with water, and this solution yields the reaction of pyrocatechin.

Chemical Characters and Relations of Pyrocatechin.

As the name indicates, the substance is obtained by the dry distillation of catechin and other vegetable extracts, and of wood. (Boiling of a concentrated solution of grape sugar with caustic potash is also said to yield it, but the relative experiments are so inconclusive that the matter is doubtful). The distillate is evaporated to crystallisation; the crystals are pressed, dried, and then repeatedly sublimated, until they are quite colourless, and no longer become coloured on exposure to air. They are broad, white shining laminae, resembling benzoic acid, which melt at from 111° to 116° , and volatilise; the substance fused in quantity boils at between 240° and 250° , and yields colourless vapours, which condense into a quickly crystallising oil.

Its taste is sharply bitter and burning. Mixed with hydrochloric acid it colours fir-wood violet. With aqueous caustic alkalies or alkaline carbonates it forms a mixture which is yellow at first, then becomes greenish-yellow, and lastly brown or black. The change of colour progressing from the surface of the liquid downwards, is accompanied by rapid absorption of oxygen. The aqueous solution of pyrocatechin produces a greenish precipitate with silver solution, the silver being partly reduced; it forms a dark brown precipitate with solution of gold, and reduces platinic chloride. It reduces alkaline tartrate of copper solution on boiling, giving a red precipitate of cuprous oxyde, and a supernatant dark green liquid. It colours ferric salts dark green, and then forms a black precipitate; the dark green colour is changed by alkalies, even in very dilute solution, to a beautiful violet-red, like that of permanganate of potash, and the green colour is restored by acids if added immediately. The test is best observed in very dilute solutions. Pyrocatechin dissolves very readily in alcohol, less readily in ether. It does not precipitate gelatin or the salts of quinine.

Pyrocatechin and Lead.—The watery solution of pyrocatechin forms, with neutral acetate of lead, a thick white precipitate, which is permanent in the air, nearly insoluble in water, but readily soluble in acetic acid. Its composition is $C_6H_4PbO_2$.

which requires 70·89 per cent. PbO . Pyrocatechin is therefore a dibasic, though weak acid. This reaction may therefore be used in processes for its isolation from animal liquids.

Diagnosis and Significance of the Presence of Pyrocatechin in Urine.

When horses' urine is allowed to stand exposed to the air for from one to three days, it may be observed that it becomes coloured dark to nearly blackish-brown on the surface; the coloration decreases downwards, and the lowest layers of the liquid present the original light colour of the secretion. This process is now explained as being the result of the oxydation of pyrocatechin by the oxygen of the air. The urine must be alkaline for the reaction to take place.

Human urine when made alkaline and exposed to the air does not ordinarily show this coloration; but when it has been decomposed by thorough putrefaction, the light-coloured liquid on exposure to air becomes brown. This reaction also is now explained as being due to pyrocatechin, at least in all those cases where the urine which shows the phenomenon also yields pyrocatechin to ether, or gives a violet reaction with ferric salt, which disappears by acidification with acetic acid. It is therefore probable that the pyrocatechin in putrid human urine is a product of the decomposition of a more complicated body at present unknown.

The urine of dogs fed upon flesh does not yield pyrocatechin. But when pyrocatechin is added to the food it reappears in the urine in the combined state, as Baumann supposes in the form of pyrocatechin-sulphuric acid. From this it appears not impossible that this body may be urophanic, and mainly derived from the food, at least in herbivorous animals. But when it appears in human urine, it seems to be a specific product of diseased action.

The observation which led to the discovery of pyrocatechin in urine is the following one, reported by Ebstein and Müller, l. c. :—A boy was shortly after his birth seized with jaundice, but recovered. There remained, however, a peculiarity about his urine, consisting in this, that though evacuated almost colourless, it assumed a purple colour on standing. This was during the first year of his life; about the age of eighteen months the urine became brown on standing. The fresh urine when mixed with alkali became brown from above downwards, oxygen being absorbed; it strongly reduced solution of silver, and alkaline solution of copper. The condensed urine yielded an ether extract, which, when re-dissolved in water, gave all the reactions characterising pyrocatechin.

CHAPTER XIII.

PHENOL-PRODUCING SUBSTANCES—PHENOL— SULPHURIC ACID, $C_6H_5SO_3$

INTRODUCTION.

FRESH human urine contains no phenol in the free state. This can be proved as follows:—On adding to 20 c.c. of the urine saturated bromine water until the mixture is strongly yellow from excess of bromine, no precipitate or turbidity is observed. But on adding to the mixture one milligramme of phenol dissolved in water, a white precipitate is immediately produced, and, on standing, settles in the liquid. If, therefore, the urine contained as much as one part of phenol in twenty thousand, the bromine would directly indicate it by forming the insoluble tribromophenol or terbromo-carbolic acid. Any phenol, therefore, which is obtained from urine which does not in the fresh state give a turbidity and precipitate with bromine water, is a product of the process applied to it, and not an educt. Phenol was first extracted from the urine of man, the horse, and the cow by Städeler ("Ann. Chem." 67 (1848), 360; 77 (1851), 17). The questions of its normal presence in human urine, of the state in which it was present, of its absorption into the circulation when applied to the skin or introduced into the stomach, have engaged many observers, to be mentioned in the sequel. But the question after the phenol-producing substances received its first more precise answer by the discovery of Baumann (Pflüger's "Archiv." 13 (1876), 247) concerning the presence in the urine of horses of a compound of phenol and sulphuric acid, a compound which he also found to be excreted by persons who were being medicinally treated with phenol. A second form in which phenol circulates in and leaves the human and animal body has been recognised, and now awaits further investigation.

History and Literature of Phenol, or Carbolic Acid, C_6H_5O .

Phenol was discovered by Runge ("Poggend. Ann." 31 (1834), 69; 32, 308) in coal-tar; recognising its feebly acid properties, he described it as carbolic acid. Laurent ("Ann. chim." (3) 3 (1840), 195) obtained this acid, which he termed

phenic, pure, and determined its properties with greater accuracy. He also discovered the tribrominated compound, which was first employed by Landolt ("Berlin. Chem. Ges." 4 (1871), 772), for isolating minute quantities of phenol from watery liquids.

Occurrence.

It is found in large quantities in coal-tar, whence it is extracted by various processes of wholesale manufacture. Before it was produced in the crystallised state it sometimes did, but does not now, pass in commerce under the name of creosote, although its properties differ considerably from those of true creosote obtained by the distillation of beech-wood. According to Wöhler it occurs in castoreum together with salicine. The circumstances under which it is obtained from the urine of man and animals seem to vary, as will be shown in the following pages. It seems to be in a small degree urophanic, that is to say, to reappear in faint traces as such in the urine after it has been ingested by the mouth or applied to the skin, while the greater part ingested seems to undergo combination. It is formed during the destructive distillation of a number of well-defined vegetable principles, such as salicine and salicylic acid, and of some compound resins.

Mode of Obtaining Phenol Pure.

Coal-tar is subjected to fractional distillation, and the products which pass over at 150° to 200° are collected and mixed with a solution of caustic potash, saturated while hot, and some additional potash in the form of powder. The greater part of the oily liquid thereupon becomes a white solid mass, which is separated from the portion which remains liquid, and dissolved in water. This solution separates in two layers—an upper light and oily one, which is removed, and a lower, heavy aqueous solution of phenol in potash. This on neutralisation with hydrochloric acid gives up phenol as an oil, which, after digestion with calcic chloride, is distilled. The distillate, on being allowed to cool slowly while protected from contact with moisture, deposits on exposure to a temperature of -10° large crystals of phenol, which may be separated from the fluid part, again crystallised, and are then ready for use.

Mode of Showing the Presence of a Phenol-Forming Substance in Human Urine.

The urine is evaporated and treated with hydrochloric acid and ether in the manner described for the separation of hippuric acid. The filtrate from the crystals of acid on addition of water becomes turbid, and deposits drops of an oily nature. These on paper cause a greasy stain, and become brown after some time.

They are soluble in hot water, and on gentle evaporation are again deposited as oily drops. They cause precipitates in solutions of nitrate of silver and suboxyde of mercury, which on boiling become black. The original mother-liquor of these drops gives all the reactions of formic acid, with this difference, that the black precipitates in silver and mercury solutions are not granular or pulverulent as after the decomposition of formiates, but flaky and bulky, showing that a voluminous product of decomposition adheres to the reduced silver. The solution also yields a precipitate with chloride of iron, and a slight excess of this reagent produces an intense and lasting brownish-red coloration. When the liquid which gives these reactions is distilled with dilute sulphuric acid, a distillate is obtained which smells of phenol, and gives with bromine water tribromophenol. This, on treatment with some sodium amalgam, gives a solution of phenol, from which the latter can be obtained by extraction with ether. 200 c.c. of human urine, acidified with tartaric acid, and distilled to one-half, gave a distillate from which two portions of ether extracted no matter, which after distillation of the ether gave any reaction for phenol (Salkowsky, Pflüger's "Archiv." 5 (1871), 351).

Mode of Obtaining Phenol from Urine of Horses.

The acidified distillate from quite recent urine from horses does not yield the reaction for phenol either with excess of bromine water or with ferric chloride (Buliginski, in "Med. Chem. Unters." 2, 234). Phenol is therefore not in solution in this urine. The addition of acetic acid to the urine before distillation does not cause any evolution of phenol, so that this body cannot be present in combination with alkali. When the urine is not quite fresh, or has been acidified by a mineral acid, a distillate is obtained, which after repeated rectification gives the tests for phenol by ferric chloride and the fir-chip (Lieben, "Ann. Chem." 1870, suppl. band, 7, 240), or by bromine-water. The quantity of phenol can be determined by causing the distillate, after rectification over sodic carbonate, to stand with an excess of bromine-water, collecting the precipitate on a weighed filter, washing it, drying over sulphuric acid in vacuo, and weighing it. By deduction of the filter from the entire weight that of the tribromophenol is obtained, and by deducting from this three atoms of bromine, and adding three of hydrogen, the weight of the original phenol is obtained.

Mode of Isolating the Phenol-Forming Substance from the Urine of Horses.

The urine is evaporated as far as possible and treated with absolute alcohol, which leaves the phenol-forming body undis-

solved. The residue is now dissolved in little water, and mixed with spirit of wine; the phenol-forming substance now remains dissolved, while a great part of the salts remains insoluble. This solution is again evaporated as far as possible, and again treated with absolute alcohol, which again leaves the phenol-forming body undissolved. This residue is again dissolved in water and spirit, and treated with an alcoholic solution of oxalic acid as long as a precipitate is produced; this is filtered off, and the solution is oversaturated with baryta. The filtered solution is again concentrated, extracted with alcohol of 90 per cent., and this extract evaporated to a small bulk. After standing for some weeks in the cold, this extract becomes a radiated crystalline mass (Baumann, Pflüger's "Archiv." 13 (1876), 289). Another process by the same observer is the following:—The urine of horses is evaporated to a syrup, and extracted with spirit of wine. This extract is exposed to the cold of frosty winter nights, when crystals are formed, which float as shining scales in the fluid. The crystals are collected on a calico-filter, pressed between blotting paper, and crystallised repeatedly from water and from strong spirit of wine. They then appear as pearl-white scales, and are the potassium salt of the phenol-forming substance. They are soluble in about ten parts of cold water, less soluble in spirit of wine, almost insoluble in cold absolute alcohol, and only less insoluble in boiling absolute alcohol. If the solution has a blue fluorescence, it is not yet pure; the solution of the pure substance does not fluoresce. The fluorescent impurity is more soluble than the phenol-producing body, and can be best removed by repeatedly extracting the crystals or powder with a quantity of water insufficient for complete solution. The substance is a compound of phenol, sulphuric acid, and potash, and yields when most pure, on analysis, the following quantities of elements:—

	Found.	Required by $C_6H_5KSO_4$
C	34.6 per cent.	34.0 per cent.
H	2.7 "	2.3 "
K	18.1 "	18.4 "
H_2SO_4	45.1 "	46.2 "

This salt is therefore phenol-sulphate of potassium. It shows the following reactions:—Equivalent quantities of the salt, caustic potash, and iodide of methyl in absolute alcohol, heated in a sealed tube, yield at a temperature little above 100° sulphate of potassium, phenol, and unchanged iodide of methyl, *but no sulphite*. This seems to exclude the presence of phenyl-sulphuric acid. When the salt is fused with caustic potash, sulphite of potassium is formed, but only in small quantity; by far the greater part of the sulphur is present in the fuse as sulphate.

The solutions of the salt give no colour reaction with ferric chloride. The dry salt, mixed with concentrated hydrochloric acid, is decomposed in the cold completely, yielding phenol and sulphuric acid. When the salt is gradually heated in a watch-glass to 170° – 180° , vapours smelling of phenol are evolved; a somewhat coloured residue remains, consisting exclusively of potassic sulphate. When the salt is quickly heated in a sealed tube, or even in an open test tube to 170° – 180° , until it begins to fuse, it is transformed into another crystallisable salt, the watery solution of which does yet in great dilution give a blue violet reaction with ferric chloride.

Mode of Obtaining Phenol from Urine of Cows.

Städeler obtained phenol from this fluid by first removing hippuric acid in the usual way with lime and hydrochloric acid. The mother-liquor he subjected to distillation, and the distillate to repeated rectification. The rectified fluid was distilled over hydrate of potash, the residue was partly saturated with sulphuric acid, again distilled, the distillate rectified over chloride of sodium, and saturated with carbonate of sodium. The oily matter thus separated was taken up with ether, the ether evaporated, and the residue again distilled over potash; the rest of the acid was evolved from the potash by the addition of bicarbonate of potassium. By continued fractional distillation he obtained almost pure phenol, mixed however with some taurylic acid or cresol. In this process the phenol is probably derived from substances similar to those contained in the urine of horses.

Physical and Chemical Properties of Phenol.

Phenol appears at the ordinary temperature as a firm colourless substance, crystallised in long prisms. The crystals fuse at 34° , forming a clear fluid, which becomes a solid again at 15° . In its crystallised state it quickly absorbs water vapour from the atmosphere and deliquesces. The slightest admixture of moisture prevents its crystallisation, even at the temperature of freezing water. In the fluid state it strongly refracts light, has a peculiar smell, similar to creosote and castoreum, and a burning taste. It is little soluble in water, requiring twenty times its weight at 20° for solution, but can be mixed with alcohol and ether in all proportions. In acetic acid it is also somewhat soluble. Its sp. gr. at 18° is 1.065. It boils at 188° , and can be distilled unchanged. It does not redden litmus, and on paper produces a greasy stain, which disappears on exposure to air. Heated to a high temperature, it takes fire and burns with a sooty flame. A few drops of it are a fatal dose of poison for a dog, and a larger quantity applied to the skin of a dog, or of a human being, also produces symptoms of poisoning and death.

It dissolves iodine with a reddish-brown colour, without thereby changing its composition. It also dissolves sulphur; but when this solution is boiled, sulphuretted hydrogen is disengaged, and on subsequent cooling a firm white matter is obtained. It dissolves several resins, and precipitates albumen in very dilute solution. This precipitate is soluble in an excess of albumen. Solutions of gelatine are also precipitated by it.

In order to identify small quantities of phenol, moisten a chip of white pine wood with the supposed phenol or its watery solution, and afterwards with hydrochloric acid. After drying, and in the course of about half an hour, the chip will assume a blue colour. Städeler recommends to expose the chip to the rays of the sun, when the colour will appear in a few minutes. The colour is not destroyed, but only bleached a little by chlorine, and the renewed application of hydrochloric acid will make it appear in its former intensity. It is necessary to test the wood to be employed with hydrochloric acid alone, as some descriptions of pine give a blue colour with the acid alone, without the intervention of phenol. Other kinds of pine-wood do not yield the coloration even with undoubted phenol, and these must also be rejected.

Another characteristic test for phenol is the violet-blue coloration which it assumes when mixed with some ferric chloride. The mixture after some standing deposits a light-coloured precipitate. The simplest reaction for phenol is its intense and peculiar odour.

Phenol is rapidly changed by oxydising agents. It reduces the oxydes of mercury and silver, leaving metal. In the solution of nitrate of silver and nitrate of suboxyde of mercury, it produces white precipitates, which become black on boiling. In a solution of mercuric bichloride it causes a deposit of calomel on standing. Indeed, most of its reactions are so similar to the reaction of formic acid that it may easily be mistaken for it, or for sulphurous acid, from which the immediate black precipitate in nitrate of suboxyde of mercury would, however, distinguish it, which belongs to sulphurous and not to formic acid or phenol. The reduced black precipitates of phenol in mercury and silver salts are flaky and bulky, and do not settle so quickly or to so small a bulk as the metals reduced by formiates.

Mixed with lead peroxyde, phenol is oxydised. This oxydation is most intense when the phenol is dissolved in acetic acid. Chromic acid quickly oxydises and colours it black.

Nitric acid transforms it under evolution of red vapours into dinitrophenylic and trinitrophenylic, or picric acid, a brown resin and oxalic acid being collateral products of the reaction.

Chlorine gas conducted into phenol, or applied to it in the nascent state, by digesting it with potassic chlorate and hydro-

chloric acid, transforms it into a mixture of several acids, containing two, three, or four atoms of chlorine, in place of as many atoms of hydrogen, dichloro-, trichloro-, and perchloro-phenol.

Concentrated fuming sulphuric acid dissolves phenol in the cold, under evolution of some heat, and deposits it again upon immediate dilution with water. But when the solution has been allowed to stand for twenty-four hours it can be mixed with water without anything separating, and then contains a sulpho-phenylic acid, $C_6H_5SO_4$.

The lead compound of such an acid was produced by Städeler with the product of distillation from cows' urine. The acid was boiled with plumbic carbonate; the filtrate, which was neutral, was evaporated in the vacuum, and when it had transformed into an amorphous mass, was dried for a long time at 100° – 110° . At first only water escaped, afterwards the odour of phenol became perceptible. At this point the salt was considered dry and analysed. It yielded 55.11 per cent. of lead sulphate, the formula $2(C_6H_5SO_4), Pb$ requiring 54.47 per cent.

Potassium and sodium slowly decompose phenol; on warming, hydrogen is evolved, and a compound of oxyde of phenol with potassium or sodium is formed, which is soluble in water. The same compound is produced by heating phenol with hydrate of potash.

A good reaction for carbolic acid is the following:—To the liquid to be tested one-quarter of its bulk of ammonia is added, then a few drops of a solution of chloride of lime, containing one part of bleaching powder in twenty of water, and the mixture is gently warmed. If sufficient phenol is present, the mixture becomes blue immediately; if the solution is dilute, the reaction appears only after some time; 5 c.c. of a solution containing one part of phenol in 4000 water will yet give the test.

Bearing of Phenol in the Body of Animals.

Some of the results of the application of phenol in the shape of tar, or impure carbolic acid, or creosote, will be described under the chapter referring to the latter body. In this place I intend to refer to the results of experiments made with the pure phenol.

Kohn ("Arch. Dermat. & Syph." 1, 224) and Almén ("Zeitschr. Analyt. Chem." 10, Heft. 1) stated that when phenol was taken into the stomach in cautious doses it reappeared in the urine. The form was implied to be the free uncombined state; but E. Salkowsky (Pflüger's "Archiv." 5, 355) showed that it was combined in some manner. Hoppe-Seyler (*ibid.* 470) showed that phenol applied to the skin was easily absorbed, and could be reobtained from different organs, and

from the urine by distillation with sulphuric acid, and confirmed in this respect the earlier experience concerning the endermatic application of tar. He applied phenol to the abdomen, or the thighs, or ears of dogs, and found that poisonous effects were produced in a few minutes. When the symptoms were at their height, the animals were bled to death, and their parts cautiously separated and examined. The blood was mixed with dilute sulphuric acid, and one-fifth of the bulk of the mixture abstracted by distillation. The distillate was rectified over dry sodic carbonate, and then treated with bromine water as above described. The amount of phenol thus obtained in one case was 0.00128 per cent. of the blood; in another, 0.00369 per cent. The brain in the first case yielded 0.00325 per cent., in the second, 0.00340 per cent. phenol. In the second case, liver and kidneys were also examined, and the distillates from them gave—liver, 0.00125 per cent. of weight of liver; kidneys, 0.00423 per cent. of their weight in phenol. From the first case it is evident that the brain contained about three times as much phenol as an equal weight of blood, and therefore, that nerve-matter exerts a selective attraction upon phenol. The second case shows the same, though in a less degree as regards the brain; the liver contained only one-third of the quantity found in an equal weight of blood, and therefore seems to exert, if any, only a small amount of selective attraction. But the kidneys seem to exert the largest amount of selective attraction, containing about a quarter more phenol than an equal weight of either blood or brain. This selective attraction of the kidneys is the main cause of the relatively quick elimination of the phenol; for when phenol is given to patients in doses of from 0.3 to 0.9 gm. per day, or applied to their skin in quantities double or treble the quantities given internally, it quickly appears in the urine in such a manner that it can be obtained from it by distillation with a mineral acid. When the use of the phenol is suspended it disappears from the urine in from one to three days, the normal traces only being afterwards obtainable. The introduction of phenol into the body causes the urine to be coloured afterwards from olive-green to dark brown, in a proportion of, but not in all cases. The brown colour appears more frequently after endermatic application than after internal use. Its specific cause is not yet explained. According to Baumann (l. c. p. 293), phenol introduced into the animal body is there united with sulphuric acid, and appears in the urine in the same combination as that naturally formed in it. This may be recognised by the increase of that quantity of sulphuric acid in the urine, which cannot be precipitated by baryta salts without previous decomposition by boiling with mineral acid. Thus a person who had been treated with phenol

discharged sulphuric acid directly precipitable, 0.148 gm. in 100 c.c.; sulphuric acid contained in compounds, which had to be decomposed by boiling with hydrochloric acid (supposed to be phenol-sulphate of potassium), 0.095 gm. Another excreted 0.046 gm. H_2SO_4 precipitable, and 0.225 gm. combined. He even says that the combined sulphuric acid could rise to from ten to fifteen times the amount of the precipitable sulphuric acid present in the form of inorganic salts. He endeavoured to prove this hypothesis by an experiment upon a dog, and an observation upon a patient. A dog voided urine which contained in 100 c.c. 0.262 gm. of precipitable, and 0.006 gm. of organically combined H_2SO_4 . His back was then painted with phenol, and eighteen hours afterwards he voided urine, in which the proportions were reversed, the precipitable H_2SO_4 being 0.004 gm., and the organically combined being 0.190 gm. in 100 c.c. In consequence of the introduction of phenol, the normal H_2SO_4 falls from 262 to 4, the organically combined rises from 6 to 190.

The urine of patients who had been treated emdermatically with phenol was evaporated to a syrup, extracted with alcohol of 90 per cent., treated with an alcoholic solution of oxalic acid as long as this produced a precipitate, and then shaken with an equal volume of ether. The mixture was then filtered, neutralised with potassic carbonate, and evaporated to a small bulk. Again taken up with alcohol, some oxalate and carbonate of potassium were separated. Again evaporated to a syrup, the solution on standing for some days in the cold deposited small scaly crystals, which were purified in the same manner, and then assumed the appearances of the crystals obtained from normal horses' urine. Some crystals could yet be obtained from the first mother-liquor by treating it with basic lead acetate, filtering, removing lead from the solution by hydrothion, and evaporating it again to a syrup. To isolate the crystals formed in this it may be shaken with ether and allowed to stand. The crystals become suspended in the ether, and can be filtered off, and obtained pure by recrystallisation. The crystals obtained from the urine of these patients were phenol-sulphuric acid, and gave on analysis mean 46.25 per cent. H_2SO_4 , and 18.5 Ka, while $\text{C}_6\text{H}_5\text{KSO}_4$ requires 46.2 per cent. H_2SO_4 and 18.4 per cent. Ka. The colour which this salt gives with ferric chloride is more of a red-violet, while the salt from horses' urine becomes blue-violet.

The urine which men or dogs discharge, after having been treated with phenol, also yields a small quantity of a blue pigment. 100 c.c. of the urine are acidified with acetic acid, and filtered through a small filter. The brownish-yellow precipitate is washed with water, and then treated with warm dilute hydrochloric acid. A skye-blue solution is formed, and soaks and

passes through the filter, and retains its colour for many weeks. From Baumann's experiments it appears that the principal condition of the formation of phenol-sulphuric acid in the animal body is the simultaneous presence of sulphates of the alkalies and of phenol. Phenol-sulphuric acid is, however, not the only form in which phenol appears in the blood and the urine; there is another compound present in both, which may yield more phenol than corresponds to that combined with sulphuric acid. This compound has not been isolated.

Phenol-sulphate of potassium exerts no poisonous action in the body. Consequently, in cases of poisoning by phenol, potassic or sodic sulphate should be given, together with albumen, milk, or other direct momentary antidotes, in order to assist the organism in the neutralisation of the absorbed portion of the phenol.

CHAPTER XIV.

CRESOL-PRODUCING SUBSTANCES.

INTRODUCTION.

LIKE phenol, cresol or cresylic alcohol, or taurylic acid, C_7H_8O , is not a normal ingredient of the urine of either man or animals, but is educed by some of the processes which educe phenol. The body from which it is educed has not yet been isolated.

History and Literature of Cresol, C_7H_8O .

Cresol was discovered in the tar obtained during the dry distillation of beech-wood by Reichenbach in 1832 ("Schweigger's Journ." 66, 301 and 345; 67, 1 and 57; 68, 352). For many years it was confounded with phenol, until Gorup-Besanez ("Ann. Chem." 78 (1851), 231; 86 (1853), 223) and Voelckel ("Ann. Chem." 86 (1853), 93; 87 (1853), 306) showed its peculiarities. But nevertheless the elementary composition of cresol was not determined until Williamson and Fairlie ("Chem. Soc. Quart. Journ." 7, 232), extracted from coal-tar creosote a homologue of phenol, of the composition C_7H_8O , which presented all the characters of Reichenbach's creosote from beechwood-tar. They termed it hydrate of cresyl, and observed that during its distillation from vessels to which the air had access, it was partially oxydised, the boiling-point falling, a small quantity of black matter forming, and phenol being evolved. Städeler ("Ann. Chem." 77 (1851), 17) obtained a body from the urine of man and animals by the same process which yielded him phenol, termed it taurylic acid, and determined its composition by the analysis of its copula with sulphuric acid. Kolbe and Lautemann ("Ann. Chem." 115 (1860), 203), by treating cresol with potassium in a current of dry carbonic acid, compounded a new acid, cresotinic, $C_8H_8O_3$, which stands to cresol in the same relation as salicylic acid to phenol, being produced by the direct combination of a molecule of carbonic acid with one of cresol, as salicylic acid is produced by the direct combination of carbonic acid with phenol.

Mode of Obtaining it Pure.

(a.) From raw creosote from wood-tar. The raw creosote, which is mostly produced in Bohemia, and of which large quantities are brought into trade by Batke of Prague, is subjected to fractional distillation. It begins to boil feebly at 90° , and a milky fluid containing water and a light stinking oil passes over. While the boiling continues the thermometer gradually rises to 160° , and the boiling now ceases for some time. The distillate which has passed between 120° and 160° is clear, and has a smell which differs from that of the raw creosote. At 190° the ebullition becomes again stronger, and a fluid rapidly distils over in oily streaks, while the thermometer remains stationary at 203.5° for some time. The temperature of the vapour then rises to 208° , and during the distillation of the last portion to 216° .

The matter which distils between 203° and 208° , and which amounts to the greater part of the whole, is collected in a separate vessel, rectified, digested for some days over chloride of calcium in a closed vessel, and again distilled.

(b.) From the raw carbolic or phenylic acid, commonly termed creosote, obtained from coal-tar. The portions of this matter which distil between 200° and 224° are collected separately, and repeatedly rectified, until a produce is obtained which boils at 203° . This must be repeatedly rectified in an atmosphere of hydrogen, as without that precaution a part of the matter is decomposed and a black matter separated. What passes below 200° is removed, and only the product passing at 200° is retained, which corresponds to the product passing at 203° , when distillation is performed without the precaution of an hydrogen atmosphere. A similar depression of the boiling-point by 3° during distillation in an atmosphere of hydrogen is observed with phenol.

(c.) The mode of obtaining from the urine of man and animals is the same as that of phenol, with which it is mixed. A black matter is deposited on first distillation resembling that deposited by creosote distilling in air. From phenol taurylic acid can be separated by combining both with fuming sulphuric acid, in which taurylic acid crystallises while the phenylic compound remains fluid.

Physical and Chemical Properties.

The pure cresol is an oily, colourless fluid, which becomes a little dark by keeping; it strongly refracts light, has a peculiar smoky odour which differs greatly from that of phenol, and a biting burning taste. It is little soluble in water, but can be mixed with ether, alcohol, and sulphide of carbon in all propor-

tions. In common acetic acid it is somewhat soluble, if concentrated in all proportions. Its sp. gr. at 11.5° is 1.04; it boils at 203° in air, at 200° in an atmosphere of hydrogen, without decomposing. It does not solidify even at any low temperature. Ignited it burns with a dense lighting flame. It is as insoluble in liquor ammonia as phenol.

The changes which cresol undergoes in contact with oxydising agents are very similar to those which are produced with phenol. The products of this oxydation are little understood, but their investigation is of importance for the chemistry of the urine, as we meet with them so frequently during our chemical operations upon this fluid.

Reactions of Creosote.

The specimen, officinal, had a yellowish colour. It was shaken with water, and the solution filtered from the milky mixture. This is termed saturated aq. solution.

Chloride of iron gives a blue precipitate, which in an instant transforms into dark brown. Boiling makes the mixture darker, and on the top a liquid resin collects. This dissolves in more water on boiling. On cooling the precipitate forms again. The diluted solution, hot, gives only a violet colour on addition of ferric chloride, which before the fluids are fairly mixed becomes dark brown. On cooling the fluid becomes smoky, and a precipitate falls.

Nitrate of silver produces a very slight opalescence, but no precipitate in the solution of creosote. On heating the fluid becomes at first smoky, then a slight dark precipitate ensues, which coalesces to dark flakes, until at last the entire fluid is quite black and opaque, even the flocks disappearing from sight. Some silver is deposited upon the glass of the tube, little quite at first, more at a later stage. Agitation and more boiling cause the precipitate to collect in flakes; the fluid remains reddish. It now bumps violently on heating, even after addition of water, and fluid is thrown out every time it is attempted to heat it. The addition of water has the advantage of collecting and stiffening the black precipitate. On standing the glass becomes covered with a metallic mirror, and the precipitate appears like a silver tree. Mercury subnitrate added drop by drop causes a white turbidity, which disappears on shaking and the addition of a few drops more, and does not reappear on further addition of reagent. Boiling produces a red fluid and a deposit of metallic looking matter upon the glass. When more mercurial solution is added no reaction is apparently produced. On heating the solution becomes pink. On longer boiling a metallic pellicle and a little of a black precipitate at the bottom of the fluid are formed.

Mercury nitrate produces no immediate reaction in the cold. But on gentle warming the fluid assumes a beautiful red colour from above downwards, which becomes very intense. On boiling a red precipitate forms, which quickly becomes dark and metallic looking. The fluid becomes turbid on cooling. On dilution much matter is yet deposited in red flakes. The bulk of the deposit remains red.

Corrosive sublimate produces no change even on boiling.

Acetate of mercury produces no reaction. A solution of chloride of sodium added to the mixture produces a white turbidity. Nitrate of baryum added and boiled produces a copious flaky flesh-coloured precipitate, similar to that which acetate of mercury produces in urine treated with nitrate of baryum. Fluid and precipitate soon become dark. The addition of much water prevents continuance of reduction.

On boiling red oxyde of mercury (obtained by heating the subnitrate) in the watery solution of creosote it becomes flaky, and it seems as if the substances simply combined. The supernatant water is colourless. The precipitate after washing is brownish-red.

Pure creosote heated with red oxyde on sand-bath until vapours of creosote begin to ascend forms a beautifully red fluid and a reddish-grey deposit. The fluid is soluble in alcohol. The grey deposit rubbed upon bright copper amalgamates it.

Neutral acetate of lead produces immediately a very slight white precipitate, soluble in excess, soluble on heating, reappearing on cooling. In a dilute watery solution of creosote acetate of lead produces no turbidity.

Tribasic acetate of lead in quantity causes a milky turbidity, or rather strong white opalescence. The fluid remains translucent, and even after boiling no molecular precipitate is visible, but after twelve hours' standing a white deposit is found at the bottom of the tube.

Boiling with peroxyde of lead produces flakes on the surface, and the fluid becomes yellow.

Chromic acid colours the watery fluid blackish-red, and makes it impervious to light. Heating produces reaction, apparently evolution of gas. Immediately after the product becomes solid, so that the test-tube can be turned upside down, without anything flowing out of it. The addition of water shows the product to be an immensely bulky precipitate, quite out of proportion to the small quantities of reagents employed.

One drop of the saturated solution of creosote boiled in solution of chromic acid, so dilute as just to show a yellow colour, becomes yet dark red. Both reagents added in small quantities at intervals produce a solution becoming darker every moment, and on cooling producing a deposit of a dirty brown colour.

A mixture of carbonate of ammonium and indigo solution is not changed in colour by creosote solution on boiling.

A dilute solution of permanganate of potash is immediately discoloured by solution of creosote, becoming first brown, then yellow, and forming a precipitate. On heating the solution becomes colourless, and a reddish-brown deposit collects on the top, which afterwards sinks to the bottom.

The watery solution of creosote produces no reaction with pure sulphate of suboxide of iron. Boiling produces a slight fawn precipitate. A brown solution of sulphate containing oxide produces an immediate precipitate, which by boiling becomes more copious.

A chip of pine-wood (cut from dry, white deal), after moistening with the watery solution of creosote and next with hydrochloric acid, on drying assumes a very feeble hue of green. The wood does not assume any coloration by hydrochloric acid alone.

Concentrated nitric acid transforms creosote into a resin, which is at first red, ultimately blackish-brown. The same transformation is effected by nitric acid in dilute solutions on long standing.

Fuming nitric acid, mixed with creosote drop by drop in a vessel which from the outside is kept cool by ice, produces at first a dark red coloration, and when an equal volume of the acid has been added, the mixture separates in two layers, an upper one of a deep red colour, and a lower black and tar-like one. The upper layer, after removal, neutralised with potash, transforms into a crystalline mass, easily soluble in hot, little soluble in cold water, which seems to have the composition $C_7H_4K(NO_2)_3O$, and therefore to be trinitrocresylate of potassium.

Chlorine or chlorate of potassium and hydrochloric acid affect creosote on prolonged digestion, and ultimately a plastic resin is produced. When chlorate of potassium is employed for the transformation it is necessary to employ great caution as soon as the product gets thick.

Concentrated sulphuric acid dissolves creosote with evolution of caloric, forming a purple-violet solution. This diluted with water, and neutralised with carbonate of baryum, yields a soluble baryum-salt, which, after evaporation, remains as a white granular matter. Its probable composition is $2C_{10}H_6Ba$. Taurylic acid from urine, when mixed with fuming sulphuric acid, on standing solidifies to a mass of dendritic crystals. It is very hygroscopic, and deliquesces. A watery solution of caustic potash causes no change. Its acid properties are those of phenol.

Black Urine after Creosote or Tar Treatment.

See the cases by M'Leod, "Medical Gazette," vol. ii. 1834-35, p. 599. Elliotson, "Med. Chir. Transact." vol. xix. p. 237. H. M. Hughes, "Guy's Hospital Rep." 3d series, vol. ii. p. 62, where also several observations of Hermann Weber are quoted. Petters ("Prager-V. J. Schrift." 1855, 3, 126) has recorded the following experience:—

In two cases of psoriasis, wood-tar was rubbed over the whole surface. Three hours after the first inunction the urine, which before had been clear and straw-yellow, became amber-yellow, and deposited uric acid in colourless plates. The urine which was passed after twelve hours was dark brownish-black, deposited a large sediment of coloured uric acid, and emitted the characteristic odour of tar. These peculiarities the urine retained during the entire course of the tar treatment.

When the brownish-black urine was left to spontaneous decomposition, which generally ensued on the fifth or sixth day, it assumed a dark green colour, on the appearance of alkalescence, and then went through all the stages of ordinary decomposition.

The urine deposited uric acid so completely that hydrochloric acid did not produce any further precipitate. After the addition to the urine of some sulphuric acid it was subjected to distillation, whereby an acid distillate was obtained, which emitted a strong odour of tar, was milky, but cleared up gradually, and deposited dark-brown drops, which were like creosote. A chip of pine-wood, moistened with hydrochloric acid, and dipped into the clear watery fluid, gradually assumed a bluish-green colour. The addition of chloride of iron to this fluid produced a dark brown mixture, and an excess of the chloride produced a brown adhering precipitate. Nitrate of silver produced a white precipitate, which, on the addition of ammonia, or simply on warming, was reduced to metallic silver. Neutral acetate of lead produced a white precipitate. When chlorine gas was passed through the fluid it assumed an orange colour, and deposited a brown resinous precipitate. The solution on the addition of nitric acid became reddish-brown; sulphuric acid produced a pink, rose colour at the bottom stratum of the supernatant fluid becoming dried like ink. Uric acid, on the influence of chromic acid the solution assumed a characteristic of carbonic acid.

The urine after the above have been in com-

ponents of tar may

The residue from filtered off yielded an

alcoholic extract, which on evaporation gave a black, tough, tar-like deposit. This, after crystallisation of the salts and resolution in alcohol, deposited a substance on the admixture of water, which had the odour of tar, was resinous, and underwent no further changes.

After repeated rectification of the original distillate, a pale, yellowish oily liquid of the odour of creosote was obtained, which, on the addition of caustic potash, transformed into a magma of white crystals, which had the smell of mint. This potash salt dissolved in water, had a very agreeable odour, and therefore must have contained *eupione*, besides *carbolic acid*. It yielded a pale, yellowish distillate, which, after removal of the water by means of chloride of calcium, became clear and colourless, of an oily consistence, and scarcely emitted any odour. It burned with a sooty flame, had a corrosive taste, blistered the skin, began to bubble at a temperature of 203° , boiled between 215° and 220° , and, with the exception of the first part of the distillate, remained fluid even at a temperature of 25° . The elementary analysis of this fluid yielded the following results:—

	Phenol	Cresol.
C = 68.55	6 C = 76.60	7 C = 77.77
H = 6.41	6 H = 6.38	8 H = 7.40
O = 25.04	O = 17.2	O = 14.83
<hr/> 100.00	<hr/> 100.00	<hr/> 100.00

From these figures follows what the high boiling-point also indicates, that the substance burned was a mixture of matters, requiring further investigation.

When the urine was neutralised with lime it yielded an ammoniacal distillate, which, after removal of the ammonia by neutralisation with sulphuric acid, left a residue from which alcohol extracted a substance having the smell of tar, and depositing in brown flakes on evaporation of the alcohol. The nature of this substance could not be ascertained any closer, as its quantity was too small. A similar substance could be extracted from the fresh urine by means of alcohol. When shaken with ether, the latter extracted from the urine a purple matter, which, after evaporation, became dark red, and was fusible.

CHAPTER XV.

CHROMOGEN OF UROBILINE.

INTRODUCTION.

THE substance here to be described was first noticed by Jaffé ("Arch. Pathol. Anat." 47, 405) in the concentrated urine of fever patients, in the spectrum of which an absorption band at the junction of green and blue was visible. It was next found that the substance could be prepared from every urine, healthy or sick, by processes to be described. Now, as healthy urine contains no substance which gives rise to any specific absorption in the spectrum, it was necessary to assume that the substance giving the spectrum is a product derived from a chromogen by the influence of acid and perhaps oxygen. The chromogen has never been isolated or analysed, and nothing can as yet be said about its nature.

UROBILINE.

This body is therefore a product and not an educt, and is not found in urine of fever patients immediately after emission, but only after some standing. It is diagnosed by the spectroscope only, and has never been isolated. The name is derived from the assumption that a body extracted from bile by hydrochloric acid and chloroform, and which has a band in the green of its spectrum, is the same as that which gives rise to the spectral phenomenon in urine. Vulair and Masius ("Centralbl. f. d. Med. W." 1871, Nr. 24) declare the colouring matter of human faeces to be identical (as far as the spectrum is concerned, which was only examined in impure solutions) with this urobiline, and Jaffé ("Centralbl." 1871, Nr. 30) has assented to this statement. It has also been stated by Maly that this urobiline, as obtained from urine, is identical with his hydrobilirubin, but this opinion I have proved to be incorrect.

Mode of Obtaining Urobiline.

According to Jaffé, the process which he has indicated produces from the urine of febrile persons pure urobiline, but when

applied to the urine of healthy persons it yields not only urobiline, but another body besides.

In order to obtain, if possible, the unmixed urobiline, I employed the urine from a case of rheumatic fever, which had yielded urerythrine. It was mixed with an excess of ammonia, filtered, and to the filtrate a concentrated solution of zinc chloride was added as long as a precipitate ensued. The voluminous reddish zinc precipitate was washed with cold and hot water until the washing water was free from chlorine, then boiled with alcohol, and dried. The dried and powdered mass was dissolved in concentrated liquor ammoniæ, and as it could hardly be filtered from insoluble impurity, was decanted, and the dark brown solution precipitated with lead acetate. The coloured lead precipitate was washed with cold water, dried, and decomposed with alcohol containing sulphuric acid. Thus an acid solution of pigment was obtained, which was brown in the concentrated state, and on dilution assumed various lighter reddish tints. Before the spectroscope the solution showed an absorption band at the confluence of blue and green, and two very faint bands, one in green, corresponding with the band of urerythrin β , and one in orange near D, corresponding with the band of omicholin. The latter was only visible with the artifice of moving the telescope to and fro. The narrow band in green pointed towards urerythrine, changed, however, by the presence of free acid. Thereupon I treated the urine from which Jaffé's precipitate by zinc had been removed, and which had lost only a portion of its yellow colour, with lead acetate as usual, until it was colourless, and treated the precipitate with sulphuric acid and alcohol; the amber-yellow solution showed the absorption band at the confluence between blue and green, just like the solution obtained by the zinc process, or any solution obtained by the lead process, but it did not show the faint narrow bands in green and orange. From these data I conclude that Jaffé's body from fever urine also is a mixture of several substances. It has no similarity that I could detect to Maly's hydrobilirubin, and on boiling with acids yields the products of the decomposition of urochrome, of which it also exhibits the aspect and odour. In its concentrated state it is black with impurity, and ill requites the great labour required in its preparation.

The two narrow bands in the spectrum were first observed by me in the present research, and have, so far as I am aware, not been described by Jaffé; certainly not mentioned by Maly. They do not occur in the hydrobilirubin spectrum.

Esoff (Pflüger's "Archiv." 12 (1876), 50) has made some experiments for the purpose of isolating urobiline, but with no success; a short note of his processes may, however, be of use to those who may like to follow the subject further.

The fresh urine was precipitated with neutral and basic lead acetate. The filtered and somewhat washed precipitate was decomposed with alcohol and sulphuric acid; the dark-coloured alcohol solution was mixed with water and chloroform, shaken, and the chloroform solution was separated by the separating funnel. The chloroform extraction was renewed as long as the solvent extracted anything. The chloroform solutions were filtered, and shaken with a large amount of acidulated water. The water now took up a quantity of urobiline, while fatty acids, fats, &c., and the greater part of the urobiline remained in the chloroform and could not be purified.

From the watery solution acidulated with sulphuric acid the urobiline was again precipitated with basic lead acetate; the precipitate was again decomposed by sulphuric acid and alcohol, the mixture extracted with chloroform in the presence of water, and the chloroform solution after separation was allowed to evaporate. The residue was red-brown, gave a larger part of a red matter to ether, and left a smaller part of an amorphous brown body, which in acid alcoholic solution showed the spectrum of urobiline.

The solutions of urobiline show the absorption band overlying F only in acid solutions. When the solution is neutralised the band disappears, but when it is made alkaline another band appears similar in width and intensity to the acid band, but moved more towards the red end of the spectrum.

CHAPTER XVI.

· OMICHMYL-OXYDE

HISTORY AND PREPARATION.

THE account which Scharling ("Ann. Chem." vol. xlii. p. 265) has given of a body which he extracted from urine, and termed "omichmyl-oxyde," is the following:—To guard against the changes which he supposed urine to undergo during evaporation, Scharling concentrated urine by freezing. The particles of ice were removed as long as they were colourless. When they became coloured yellow, the concentration was discontinued. Artificial freezing Scharling found unserviceable, as he could not succeed in making the urine freeze from above downwards, which seems necessary for allowing the solution of increased specific gravity to sink. Urine so concentrated was mixed with an equal volume of ether, and allowed to stand for twenty-four hours or more, being shaken at frequent intervals. The ether dissolved a part of the oxyde of omichmyl, a little urea, and several other matters, which were not determined. The extraction with ether was repeated several times, the ether was distilled off, and the residue was washed with cold, afterwards with hot, water. By this treatment the urea and the other matters soluble in water were removed, while oxyde of omichmyl was left. For its purification Scharling proceeded as follows:—To decompose ammoniacal salts, which he alleges to have adhered to it, it was dissolved in caustic potash, the solution heated to ebullition, and afterwards precipitated with dilute sulphuric acid. The oxyde was thereby precipitated in brown flocks. They were collected on a filter, dried, and dissolved in ether; the solution was filtered, and, after addition of a little water, was evaporated, when the pure oxyde of omichmyl remained.

Chemical Characters.

It fuses in boiling water, forming a brownish-yellow oil, which, on cooling, solidifies to a resin. It is soluble in ether, of wine, ammonia-water, dilute caustic and carbonated and soda. The solution in spirit has an acid reaction.

In its dry state it has a strong odour of castoreum; but on boiling with water, a faint urinous odour is perceived. When the ethereal solution is mixed with a very small quantity of spirit of turpentine, the mixture, after evaporation of the ether, assumes a sweetish aromatic odour, resembling the smell of urine after taking spirit of turpentine or juniper-oil internally. Heated strongly, after moistening with water, until decomposition ensues, it gives out a strong, penetrating odour of old urine. Heated more strongly, it takes fire, and burns with a white, strongly-lighting flame. Red-heat leaves only a faint trace of ash. Boiled with aqua regia, the oxyde leaves a yellow semi-fluid resin. This boiling, performed in a retort, yields a greenish-yellow oil in the receiver, together with some nitric acid and water. This oil, boiled with water, leaves a little yellow resin. The watery solution, on cooling, deposits scaly crystals, which are easily soluble in spirit, volatile, and, when saturated with ammonia, produce a red precipitate in a neutral solution of chloride of iron. This makes it probable that the acid is benzoic, which Scharling believes to have been produced by the action of nitric acid upon the oxyde of omichmyl.

The benzoic acid was, however, probably, at least in part, derived from the hippuric, with the existence of which in human urine Scharling was not acquainted when he wrote. The oxyde of omichmyl was therefore very impure, as is also evident from all other reactions. Scharling wasted much labour upon the chlorinated and nitrated bodies extracted from the mother-liquor of nitrate of urea. But, finding that his chloro- and nitro-omichmylic acid turned out to be substitution-products of benzoic acid, which he had also obtained from his oxyde directly, he, after the discovery of hippuric acid as a natural ingredient of the urine, abandoned his researches. Omichmyl-oxyde was either forgotten entirely, or dragged on a pitiful existence in the small print notices of handbooks.

I repeated the experiment of Scharling upon urine concentrated by evaporation on the water-bath. The ethereal extract yielded the oxyde, and yielded the more of it the longer it was heated by itself after the evaporation of the ether. No oxyde was obtained if all superfluous heating was carefully omitted. From this I learned that the oxyde was not contained as such in evaporated urine, and that it was formed by heating the yellow ethereal extract with hippuric acid. The yellow matter contained in the ethereal extract, after purification by boiling with dilute acids, yielded the fallow resin of Proust, or the omichmyl-oxyde of Scharling. It never yielded indigo blue.

CHAPTER XVII.

URERYTHRINE.

HISTORY AND LITERATURE.

It was first described by Proust as rosacic acid, and believed to constitute the entire bulk of the lateritious deposits. After uric acid had been found in these deposits, Prout assumed purpuric acid in combination with ammonia to be an admixture to these deposits. The subsequent observations of Fromherz, Guggert, Duvernoy, Scherer, Landerer, and Heller seemed to confirm the opinion of Proust as to the acid nature of urerythrine, but the inability of chemists to produce salts of this substance with bases speaks against that opinion. The most extensive and also the most productive researches on this substance have been made by Heller ("Archiv. Chem. Micros." vi. 361). But notwithstanding his lucid description, little attention has been paid to this substance, and this circumstance, and the various names under which it has passed, have produced some confusion regarding its identity.

Occurrence.

Urerythrine occurs in fresh urine generally in a dissolved state, and then imparts to the fluid a fiery reddish-yellow, or yellowish-red colour, sometimes mistaken for blood, or the colouring matter of medicines. It adheres to the amorphous deposits of urates, imparting to them the various shades of colours, but not to deposits of earthy phosphates.

Mode of Obtaining it Pure.

The deposits of urates with urerythrine adhering, whether formed before or after emission, are collected on a filter and washed with water, until a portion, on being burned on platinum foil, no longer evolves the peculiar odour of burned urine. A considerable loss of substance necessarily occurs with this mode of washing, as also with the subsequent washing with alcohol. After this operation the deposit is digested with warm absolute alcohol, which takes up urerythrine, and, after filtration and evaporation at a temperature not exceeding 50° C., leaves it in the form of a red amorphous residue. The lateritious deposits

may also be collected on a filter and strongly pressed, and without being washed, extracted with alcohol.

If urerythrine occurs in the urine in solution, it can be obtained therefrom by combining it with an artificial precipitate. On adding to the clear urine a little ammonia or carbonate of ammonia, so that it remains faintly acid, and no precipitate of earths occurs, and, after shaking and letting it stand for several hours, adding a few drops of acetic acid and letting it stand again, a pink deposit will form after the lapse of a short time, which is then treated like the spontaneous deposit (Heller).

On dissolving white and pure urate of ammonia in urine, which by its pink or purple colour indicates the presence of urerythrine, it is precipitated on cooling, deeply coloured by the pigment.

Urerythrine can only be obtained from such precipitates, and never by evaporation of the urine.

Physical and Chemical Properties.

Urerythrine is an amorphous, lobster-red substance. When it shows a radiary or granular crystalline arrangement it is impure. It has a decidedly acid reaction, and thus adds to the acidity of urine. It is soluble in alcohol, water, and ether, little at the ordinary temperature, more at higher temperatures. The solutions are of a pale reddish-yellow colour, which is never saturated. It burns on platinum foil without exhibiting any particular phenomena, and leaves no residue. Its solution in water is precipitated by acetate of lead, by nitrate of suboxide and protoxide of mercury, and by salts of baryta; but the precipitates are only loose combinations, and readily yield urerythrine to boiling alcohol. By dilute acids urerythrine is not decomposed. It dissolves in concentrated sulphuric and hydrochloric acids, and thereby undergoes a change.

Spectrum and New Reaction of Urerythrine.—Urine from a case of acute rheumatic fever deposited a brick-red sediment of urates, but did not itself become clear. The deposits from four days were collected on a filter, and boiled with alcohol of 86 per cent. Much of the red colouring matter, and apparently of the urates also, dissolved, and the latter were deposited in considerable quantity from the alcohol on cooling. The concentrated and cooled extract was filtered from the red deposit which it had formed, and exposed to the oxyhydrogen light before the spectroscopic. A layer of three centimetres in thickness allowed red and yellow to pass: the rest was obscured. Two centimetres showed a broad absorption in green and blue, while one centimetre showed that this broad band was composed of two separate bands. There was also a feeble narrow band between D and green. The interval between the band in blue and the dark end was fine violet. The bands were best seen when the telescope

was gently moved to and fro. The narrow band and α can be seen with an oil lamp, but β only with a good oxyhydrogen lantern. The alcoholic solution was further repeatedly filtered until it was quite brilliant, and then had a fiery-red colour, and showed the three bands most distinctly.

A diagram of this spectrum is represented in fig. 2 of the plate heading my paper entitled "Further Researches on Bilirubin and its Compounds," in "Journ. Chem. Soc." May 1875.

The deposit from the first boiling alcohol solution gave to new boiling alcohol faint traces of yellow matter, and remained orange; it then dissolved in potash with a green colour, but gave no bile-colouring matter reaction with nitric acid, and when acidulated yielded nothing to chloroform. It consisted of urates still coloured by urerythrine, as was specially proved. Urerythrine, when solid and dry, and treated with caustic potash, assumes immediately a *green colour*, and is then rapidly destroyed. Immediate acidification of the solution does not restore the urerythrine. This reaction is highly characteristic of the substance; it calls to mind some similar reactions of vegetable red colouring matters.

Diagnosis in Urine.

The pink colour of urine, and the production in it of a *light pink* precipitate by the addition of a great excess of acetate of lead, ensure the diagnosis. The precipitate produced by acetate of lead in urine destitute of urerythrine is *white*, though containing colouring matter. The filtrate from this precipitate, by boiling with hydrochloric acid, yields a test for indigogen. The presence of the same substance is indicated by the filtrate assuming a violet colour when shaken with concentrated sulphuric acid. When ether is shaken with this acid mixture it becomes red from urrhodine; and from the blue residue, indigo blue may be obtained by boiling with alcohol.

When much urochrome is present in urine, the precipitate obtained by acetate of lead assumes a bay colour without any admixture of red. An excess of this colouring matter does, therefore, not prevent the pink colour of the precipitate by lead, due to urerythrine, from appearing in cases where urerythrine is present. The colouring matter of bile stains the lead precipitate intensely yellow, and then it is difficult to prove the presence of urerythrine.

For experiment, urine from a case of acute rheumatism is best suited.

The deposits may also be examined for urerythrine by dissolving them in water, and treating the solution with acetate of lead. From this precipitate a purer urerythrine, with a less considerable loss, is mostly obtained.

In order to ensure the diagnosis of the presence of urerythrine it is necessary to bear in mind that deposits may be coloured red by the following substances :—

1. Only in strongly alkaline urine by
 - (a.) Urrhodine (colour more violet).
 - (b.) Precipitates of sennine or rheine.
2. In acid or alkaline urine by
 - (a.) Urerythrine.
 - (b.) Blood-corpuscles.

The following reactions ensure the diagnosis of these substances :—The deposit from which the fluid has been removed by decantation or filtration is shaken with ether, which assumes a violet-red colour when urrhodine is present, and dissolves the entire amount of this substance.

A part of the deposit is acidulated with sulphuric, hydrochloric, or acetic acid; if the colour is changed into citron yellow, and by the addition of ammonia back again into red, sennine or rheine are indicated.

The presence of albumen or coagulating hæmatoglobuline ensures the diagnosis of blood.

Pathology of Urerythrine.

As urerythrine does occur but rarely in healthy urine, its appearance is practically a symptom of disease. It occurs more frequently than any other abnormal substance; but, notwithstanding, its exact bearing has not as yet been ascertained.

When organic medicines and compounds, drastics, mineral salts, and solvents cause disorders of the intestinal canal or the kidneys, urerythrine does not appear in the urine. Tincture of cantharides, for example, when given in such doses as to cause albumen and blood to appear in the urine, did not make urerythrine appear in the urine. Its occurrence is rarely observed to accompany diseases of the kidneys.

The case is different, however, with metallic salts; the compounds of lead, copper, mercury, arsenic, antimony, and others, when given medicinally or ingested accidentally, even in small doses, soon cause urerythrine to appear in the urine. When taken in large doses, so as to exert poisonous effects, they cause the appearance of large quantities of urerythrine in the urine. As urerythrine frequently appears in the urine in consequence of or in connection with diseases of the liver, independent of metallic poisons, and as the latter mostly exert their first poisonous action in the liver, it becomes likely that the liver is in both cases the place where this substance is produced.

When urerythrine is present in urine, the common colouring matter is mostly present in larger quantities, as are also urea

and uric acid. The quantities of inorganic salts are variable. Any deposits that may occur assume a pink colour.

Indigogen is changing, relatively to urerythrine. In urine from cases of acute rheumatism the quantities of these substances seem to stand in an inverse proportion to each other.

Diseases in which Urerythrine most commonly occurs in the Urine.

1. *Acute Rheumatism*.—In this disease it is almost constantly present, but its quantity is often changing periodically. The earthy phosphates appear to be augmented.

Pericarditis.—When this disease sets in, the earthy phosphates mostly undergo a rapid diminution, and during twelve hours may fall from the highest to the lowest figure. Then follows sinking of the chlorides, until they disappear entirely, and some albumen mostly makes its appearance. At this stage the quantity of urerythrine present is very large.

Pneumonia, pleuritis, peritonitis, and acute morbus Brightii, when complicated with acute rheumatism, show the same course of urerythrine and other ingredients of the urine.

2. *Certain diseases of the Liver*, such as hypertrophy, induration, granular liver, are accompanied by the largest amount of urerythrine that ever occurs in the urine. Ascites, in consequence of liver disease, gives a large amount. In these cases the quantity of the phosphates is normal, and the amount of urochrome is mostly increased. The colouring matter of bile is only present in cases which are complicated by obstruction of the gall-duct.

3. *Lead-Colic and Metallic Poisoning*.—In these cases the urine is similar to that in diseases of the liver, but never contains the constituents of bile. Lead and copper, when causing disease, are *always* to be detected in the urine; the other metals in many cases. Earthy phosphates are variable.

4. *Intermittent Fever*.—The phosphates are variable; urea is mostly diminished, except during paroxysms.

5. *Diseases of the Brain*.—In acute cases of arachnitis and meningitis, the amount of urerythrine in the urine is always increased. The quantities of earthy phosphates and of urea are increased. There is little ammonia and albumen. In chronic diseases of the brain, such as hydrocephalus and tubercles, urerythrine is often present. Typhus also makes urerythrine appear in the urine, together with an excess of earthy phosphates, particularly when brain symptoms are prevalent.

CHAPTER XVIII.

UROCHROME.

INTRODUCTION.

THE matter to which urine owes either the whole or the greater part of its yellow colour I have termed urochrome ("Hastings Prize Essay of the British Medical Association," 1864). It is an alkaloid, but not of very pronounced basic properties, as has been shown in the chapter on reducine. It can now no longer be confounded with the extractive acids, kryptophanic and paraphanic, nor with the colourless substances, which, like indigogen and urrhodinogen, form pigments by chemolysis. It has been isolated, but not finally analysed. Its principal characteristic is, that on chemolysis with acids, it is split up into several bodies of smaller atomic weight, one of which, uromelanine, seems to be derived from the colouring ingredient of the blood. As pure urochrome does not show any specific absorption before the spectroscope, when strongly acidified, it is not the chromogen of urobilin, and is not derived from it. Yet urochrome gives rise, by chemolysis, to probably two or three substances having distinct spectral phenomena, which greatly aid in their diagnosis.

Earlier Researches on the Colouring Matter.

For an appreciation and interpretation of the labours of Scherer ("Med. Gazette," 1845, pp. 363, 410), Harley ("Verhandl. Würzburg Phys. Ver." vol. v. 1854), and Marcet, I must refer to the introduction to the Hastings Prize Essay, where the processes and products of these authors are described. Vogel's method of estimating the amount of colouring matter in the urine by mere shade and density of colour ("Archiv. Verein. gemeinsch. Arbeiten," 1 (1853), 137) does not appear to me to have any claim to that degree of accuracy which science demands, and I have therefore not given it in this present edition. The products of the chemolysis of urochrome were first described by Proust (in the Spanish "Annales de Historia Natural," March 1800, Nr. iii. p. 275; and in the old "Ann. Chim." 36, 258; and again in "Ann. Chim." new series, 14, 260). A full account of these results was also

given in the Hastings Prize Essay. In 1844 Liebig ("Ann. Chem." 50, 161) drew attention to Proust's papers, but without himself advancing the subject. The singular circumstance that our knowledge regarding the normal colouring matter of urine has not advanced quicker and farther than we perceive it to be, is due in the first instance to the neglect of the observations of Proust; and in the second to the negligent habit of authors of confounding the colouring matter with the chromogen's and some of their products on the one, and with the extractive acids on the other hand.

Modes of Isolating Urochrome.

1. The mode of isolating urochrome by means of phosphomolybdic acid has been fully described under the chapter referring to reducin.

2. Another mode consists in precipitating fresh urine with neutral and basic lead acetate, decomposing the precipitate with sulphuric acid, and precipitating the urochrome (and some xanthine-like body) from the filtrate, by phosphomolybdic acid.

3. A third mode is the following:—The urine is treated in the cold with excess of baryum hydrate crystals, and *after saturation with baryta*, filtered. The filtrate is treated with lead acetate solution and ammonia, until no further yellow precipitate is produced. The precipitate is filtered, washed, and triturated in a mortar with excess of sulphuric acid; the filtrate from the sulphate then shows the urobiline spectrum (spectrum 4 of plate in "Chem. Soc. Journ." May 1875). The acid solution is now treated with baryum hydrate, and any slight excess of this neutralised by a current of carbonic acid. The filtrate, if necessary concentrated, is now treated with strong alcohol, and the precipitate of kryptophanate and other matters removed by filtration. The filtrate containing the urochrome is evaporated to dryness in a strong current of air. The residue is yellow, and for the most part soluble in water, but the solution shows no particular absorption spectrum.

Chemolysis of this residue with boiling hydrochloric acid produces an immediate precipitate, which after filtering, washing and drying, yields to ether a new product resembling omicholine in all but its spectrum. The red solution showed spectrum 3 of the plate above quoted, having a distinct narrow band at the beginning of yellow, and a broader band at the beginning of blue; all blue slightly obscured, violet cut off. The residue insoluble in ether is now treated with alcohol, which dissolves the *uropittine*. This solution gives spectrum 7 of plate, having a band overlying the green and beginning of blue, faint, and of least intensity on the green side, but of deepest intensity and sharply defined on the margin towards the blue. The blue which

appears beyond the band is of the same intensity as the band itself.

4. Urine is saturated with baryta by agitation with an excess of crystals, and the filtrate is treated with lead acetate cautiously, to obtain a precipitate without neutralising the alkalinity of the liquid. This precipitate is treated with excess of lead acetate to dissolve out the kryptophanate. It is washed with water and decomposed with sulphuric acid, and may now be further treated by the phosphomolybdic acid process. It is remarkable as yielding no urobiline spectrum. Boiled with a slight excess of sulphuric acid for some time, it darkens at first, and then deposits some resinous flaky matter, which is filtered off, washed, and treated with ether. This dissolves a small portion of omicholine (see spectrum 5 of plate quoted); the residue dissolves almost entirely in alcohol, and consists of uropittin, leaving some uromelanine. The filtrate from the resinous matter is boiled for some time longer with more sulphuric acid, and furnishes a considerable quantity of uromelanine, which is dissolved in ammonia and precipitated by acid.

I made a number of experiments similar to the foregoing, with a view of ascertaining whether by fractional precipitation the yellow matter here termed urochrome could be separated into two or more yellow bodies, or a yellow one and some colourless body, and whether these could then be singly transformed into the decomposition products believed to derive from urochrome. But the experiments all gave the same results; each fraction of precipitate yielded the three products described by me above, and none yielded any substance having the slightest resemblance to hydrobilirubin. The chemical principles upon which the isolation of urochrome is based will then be easily seen to be the following:—

Precipitants for urochrome are phosphomolybdic acid in acid solution; lead acetate in acid and alkaline solution.

Phosphoric and sulphuric acid are separated at whatever stage by caustic baryta, with which urochrome forms a compound soluble in water and in spirit.

The extractive acids, kryptophanic and paraphanic, are separated either by treating the mixture of their lead salts with urochrome lead by excess of saturated lead acetate solution, which dissolves the extractive acid lead salts, while leaving urochrome lead insoluble; or by treating the mixture of their baryta salts with alcohol, when the extractive acid salts are precipitated, and the urochrome baryta dissolves.

The indigogen, and urrhodinogen, and urobilinogen, are best removed by the phosphomolybdic acid, which leaves them unaffected. This acid also enables the operator to get rid of all but traces of chlorine; but it carries a body resembling, though

not identical with, xanthine, into the urochrome, from which it is at present separated only with great difficulty.

The indigogen and urrhodinogen are also separated, at least as to their main quantity if not entirely, by precipitating the urine with neutral and basic lead acetate only, without employing ammonia for a third precipitate. It is this third precipitate which contains the main if not the whole quantity of these chromogens.

Last Purification of Urochrome.

The urochrome obtained by any of the above processes is liable to contain a trace of hydrochloric acid, and a trace of a xanthine-like body. Both these impurities can be removed by shaking the solution with freshly-prepared oxyde of silver. The silver combines with a great part of the urochrome, forming a bulky precipitate, while the urochrome which remains in solution contains silver in solution. This solution is yellow, but much brighter than before the treatment with silver oxyde; it is freed from silver by hydrothion, and the filtrate evaporated to dryness on the water-bath. Pure urochrome now remains in the form of an amorphous yellow solid matter. In this operation the quantity of silver oxyde employed must be carefully proportioned to the quantity of chlorine and xanthine-like body to be removed, and beyond this only a slight excess must be used; any great excess of silver oxyde would leave hardly any urochrome in solution, and cause the operation to fail.

Physical and Chemical Properties of Urochrome.

On evaporation of a pure and neutral solution of urochrome it remains in the form of yellow crusts. They are, however, not entirely resolvable in water.

It is easily soluble with a purely yellow colour in water, least in alcohol, more in ether, very dilute mineral acids, and alkalis.

Its watery solution, on standing, even when precluded from contact with air, assumes a darker colour, verging towards red, and becomes red at last. It next becomes turbid, and deposits flakes of resinous matter. This decomposition is effected more quickly by the agency of heat.

When a yellow, somewhat acid, watery solution of urochrome, such as can be obtained without the employment of oxyde of silver, is evaporated in the open air on the water-bath, it becomes covered with a red film of resinous matter. The fluid, on cooling, becomes turbid; but ultimately is cleared up by the deposition of more resin, which was dissolved in the hot fluid.

The same acid watery solution, evaporated in a retort in a current of hydrogen, is decomposed. Resin is formed, which is dissolved in the acid liquid with a red colour; but falls down on

cooling in the form of flakes. These under the microscope are seen to be composed of red non-crystalline granules. A highly acid, clear, colourless, stinking distillate, passes into the receiver. The ultimate residue in the retort is syrupy, and remains so when repeatedly treated with water to remove resin, and redistilled in the hydrogen current.

Acids effect a similar transformation by mere contact, immediately by boiling. Hydrochloric acid immediately precipitates resin by boiling; but retains in solution much resin, of which the greater part is precipitated by the addition of water. Dilute nitric acid also effects this decomposition; but the solution cannot be concentrated, as can the hydrochloric acid solution. The hydrochloric acid solution, after evaporation of most acid and neutralisation of residue, does not yield the reaction for sugar with an alkaline solution of copper. Boiled with caustic potash and a little oxide of lead in solution, urochrome apparently undergoes no change; no sulphide of lead is deposited.

From its watery solution urochrome is precipitated by nitrate of silver as a gelatinous mass, entirely soluble in nitric acid; neutral acetate of lead throws down a white and flaky precipitate; basic acetate of lead, a bay or yellow coloured flaky precipitate. Acetate of mercury produces a yellow fawn precipitate. Precipitation by this reagent is complete from neutral solutions. Nitrate of mercury produces a white precipitate; which, after boiling, becomes pale flesh-coloured; it is entirely soluble in nitric acid. The supernatant fluid assumes a pink colour.

Decompositions of Urochrome.

Uromelanine, Uropittine, Omicholine, Omicholic Acid.

When an acid watery solution of urochrome, or a mixture of urochrome and a quantity of mineral acid, is boiled for a sufficient length of time, the fluid assumes a dark red or brown colour, and drops of resin are seen in it. On the addition of water, or on cooling and standing, it deposits red or brown flocks, which can be worked into a lump by kneading with a glass rod, and removed. By repeating the boiling of the mother-liquid some more resin can be obtained; but the subsequent portions show already, by their black colour, that they are not so pure as the first portions.

When this resin is allowed to stand under water, or kneaded with a glass rod, a brown powder separates from it, which is evidently mechanically mixed with it. (*Uromelanine*.) This powder also remains undissolved when the resin is extracted with alcohol. Boiling alcohol dissolves a little of this brown powder, and deposits it again on cooling. If, therefore, the resin is dissolved in boiling alcohol and filtered hot, the solution has to be filtered a second time after standing for twenty-four hours.

The alcoholic solution of the resin thus obtained is of a ruby-red colour. The addition of water causes at first an opacity in it; soon, however, the greater part of the resin is deposited in the form of reddish-brown flocks. If the alcoholic solution is evaporated to a high state of concentration and poured into cold water, the resin is deposited in a granular form. If the coloured liquid is now filtered off, and the granules are agitated in hot water, they again coalesce into the original soft red resin. On drying and standing, the resin becomes hard and brittle. In hot water, it becomes adhesive, like tar, and dissolves a little. It has a peculiar powerful smell, which is evidently the basis of the smell of castoreum. Heated on platinum, it fuses; and under boiling emits a powerful and disagreeable colour. It next burns with a strongly lighting flame, and is ultimately entirely consumed. It consists mainly of three distinct substances, two of which are permanently fluid resinous substances, soluble in and extracted by ether, *omicholine* and *omicholic acid*; while a third is a permanent solid body, *uropittine*, exhibiting resinous qualities under certain conditions. Sometimes small quantities of intermediate products (*urorubine*, *meta-uropittine*, *paramelanine*) are mixed with and separated from the foregoing products, which are the main and invariable products of the decomposition of urochrome.

Mode of Obtaining Uropittine and Uromelanine from Urine directly.

The mixture of resin and black matter can be obtained from urine in the following manner:—

(a) *From Fresh Urine.*—A quantity of prepared extract of urine is put into a capacious beaker, and mixed with concentrated sulphuric acid, added, drop by drop, while the fluid is being agitated. After filtration from a slight precipitate, the fluid is diluted with water and distilled in a capacious retort. When the fluid has been reduced to one-half, the black resin will be seen adhering to the sides of the glass and to the platinum, which it is well to put into the retort to prevent bumping. The boiling is now interrupted, and the fluid allowed to cool. Fluid and resin are separated by decantation or filtration. The particles of resin are united by fusion in hot water. They are then washed, dried, and the resin is extracted from the black matter by solution in alcohol.

(b) *From Putrid Urine.*—Putrid urine is treated with a little lime in powder, or sawdust, and filtered. The dark brown filtrate is evaporated in an open dish over the free fire. Although it soon assumes a strongly acid reaction, nothing but ammonia passes away. All froth which rises during the evaporation is carefully skimmed off. When black particles begin to appear on

the surface it is allowed to cool, filtered, put into a retort, mixed with dilute sulphuric acid, and distilled. A mixture of hydrochloric, benzoic, acetic, and another acid passes over, together with a stinking matter, which deposits in flakes when the distillate is left to stand. The residue in the retort soon deposits the resin as a soft tar on the surface of the fluid, the sides of the vessel, and the platinum, put into the fluid for safe boiling. The resin is separated mechanically and by the filter, washed, and separated into its constituents by alcohol. The uropittine and uromelanine thus obtained present the same essential properties as those obtained from fresh urine.

The mixed resin obtained from putrid urine has some peculiarities by which it is distinguished from the resin obtained from fresh urine.

It has the smell of asphaltum when fresh, mixed with that of castoreum. Its taste is slightly bitter, and highly nauseous. It does not dissolve in the saliva to any great extent.

The black matter, after separation from the resin by alcohol, and purification by precipitation from potash, falls down as a bulky deposit, but shrinks on drying. It ultimately becomes hard, black, and shining, and breaks like asphalt. It differs, therefore, in its physical appearance, from the uromelanine obtained from fresh urine.

The resin, or uropittine, from putrid urine is also peculiar in this, that it is much darker than the resin from fresh urine, and contains some benzoic acid, which is never present in the resin from fresh urine. From this it can be separated by precipitating its alkaline solution by acid in hot water, collecting the resin by kneading, and decanting the liquor, which contains the benzoic acid and some resin in solution.

Volatile Oil, Acetic, and Formic Acid.—The distillate obtained in the foregoing chemolysis is acid, and of a disagreeable odour. It is neutralised with carbonate of soda, and evaporated to a smaller bulk. When it is observed to evolve a strong urinous smell the evaporation is interrupted. It is now extracted with repeated quantities of ether; the ether is distilled off, and leaves an *essential oil* as a residue; this has a powerful peculiar odour, a yellowish colour, and on mixing with water becomes milky; on being heated with nitrate of mercury it gives a purple reaction, and does not change the solution of silver even on boiling. It consequently contains no phenol or cresol, and is evidently an oil of a peculiar kind. It may be termed *the volatile oil of urine*.

The neutralised solution from which the oil has been extracted contains large quantities of *acetic* and *formic acid* in combination with the base employed. These acids will be treated of in a separate chapter. It is at present impossible to say whether

they are present in the fresh urine, or formed by the chemolysis from more complicated bodies, notably from urochrome. But it is necessary in this place to assure the reader that these substances are formed massively, so that in a larger operation I have obtained many ounces of uromelanine in a pure state, and many ounces of acetate and formiate of lead and baryta, from which the pure acids were separated by the processes to be described.

Synopsis of the Products of the Chemolysis of Urine.

A. Fixed Coloured Products of Decomposition by Sulphuric Acid.

Insoluble in ether, all soluble in ammonia.	{	Uromelanine . . .	Insoluble in alcohol.
		Uropittine . . .	Soluble, sparingly, in alcohol.
		Urorubine . . .	Soluble, easily, in alcohol.
		Metauropittine . . .	Soluble in alcohol.
Soluble in ether and alcohol.	{	Omicholine . . .	Insoluble in ammonia.
		Omicholic acid . . .	Soluble in ammonia.

B. Volatile Products of Decomposition by Sulphuric Acid.

Soluble in ether . . .	Essential oil.
As sodium salts insoluble in ether {	Acetic acid.
	Formic acid.

Chemical and Physical Character of Uromelanine.

Uromelanine is insoluble in water; very little soluble in alcohol, but imparts to this agent a dark red colour, in the cold, while it is in its bulky condition, but when contracted and pulverulent, boiling is necessary to colour the alcohol. It is very easily soluble in dilute caustic alkalies, ammonia and potash, and precipitated by any acid. From its solution in the smallest quantity of ammonia it is completely precipitated by most soluble salts of the earths and the metals. The ammoniacal solution of nitrate of silver produces no precipitate in the ammonia solution of uromelanine, but the precipitate appears on the addition of acetic acid. Uromelanine, whether prepared from fresh or putrid urine, is slightly soluble in acetic acid, more in hot than in cold; and from this solution nitrate of mercury precipitates a red matter. On dry distillation it gives out white fumes, which condense to an oil, but no sublimate of any kind is obtained. The fumes or oil are neutral, bleaching rather than changing, like acid or alkali, the colour of litmus. They give no aniline reaction, but with nitrate of mercury they give an exquisite red reaction and precipitate. A very voluminous dense charcoal of the bulk of the original particles remains.

Uromelanine dissolves in nitric acid with a dark red-brown colour. Red vapours are evolved on boiling, but the reaction is not violent even with much acid. After long boiling the solution is yellowish-red. Addition of water produces a fawn pre-

precipitate which is entirely soluble in alcohol, and with ammonia and baryum chloride gives a voluminous yellow precipitate. When the nitric acid is evaporated two matters are left, one soluble in alcohol the other insoluble. The solution gives the red reaction with nitrate of mercury.

Concentrated fuming sulphuric acid easily dissolves uromelanine, forming a red or purple solution. Immediate addition of water precipitates all coloured matter, and the liquid is white and clear. But when the concentrated mixture is allowed to stand over night, water precipitates a coloured portion; another coloured portion remains dissolved. Carbonate of baryum precipitates all coloured matter on boiling, and the filtrate is again white.

Recently precipitated uromelanine suspended in water and subjected to the action of chlorine yields a brownish substance, soluble in boiling alcohol. While the spirit is being heated, some of the substance melts to a brown resin, which dissolves by continued heating with new alcohol. The solutions added together yield on cooling yellowish-red amorphous flakes. These flakes are not again entirely soluble in alcohol, probably because the chloro-compound undergoes a change during the heating with the alcohol and subsequently. This supposition was confirmed by the results of elementary analysis.

Elementary Composition of Uromelanine.

From many analyses of four different large preparations, and from the two-thirds basic silver salt $Ur : Ag = 3 : 5$ to be described, and from the harmony in the proportion of all the salts, it follows that uromelanine is $C_{36}H_{43}N_7O_{10}$.

	Theory of atoms.	Per cents.	Found mean.
C_{36}	432	58.93	57.21
H_{43}	43	5.86	5.74
N_7	98	13.36	12.88
O_{10}	160	21.85	24.17
	<hr/> 733	<hr/> 100.00	<hr/> 100.00

Compounds of Uromelanine.

In the following I give a synopsis of the compounds of uromelanine with bases which I have produced. The numbers on the left under Ur show the number of molecules of uromelanine, the numbers under the symbol of each base the number of atoms of each base or metal contained in the compound. All compounds obtained have been analysed; all are here described, and none have been omitted.

Synopsis of Uromelanates Produced—

<i>Silver Salts.</i>			<i>Calcium Salts.</i>		
Ur	Ag	Ag found.	Ur	Ca	Ca found.
1	1	13.38 per cent.	5	2	2.03 per cent.
2	3	18.56 "	4	3	4.35 "
3	5	20.45 "	2	3	7.27 "
<i>Baryum Salts.</i>			<i>Zinc Salts.</i>		
Ur	Ba	Ba found.	Ur	Zn	Zn found.
5	2	7.20 per cent.	3	1	2.82 per cent.
2	1	9.05 "	5	2	3.54 "
4	3	13.28 "	2	1	4.42 "
<i>Lead Salt.</i>					
Ur	Pb	Pb found.			
3	2	15.70 per cent.			

Normal or Neutral Uromelanine Silver, $\text{Ur} : \text{Ag} = 1 : 1$.—A neutral ammoniacal solution of uromelanine was prepared by evaporating a dilute solution of the substance in ammonia water to dryness on the water-bath, and extracting the salt which had remained soluble from the uromelanine which had become insoluble by the loss of ammonia by means of water. This dark brown solution was precipitated by silver nitrate, the precipitate contracted by heating in the fluid, washed by decantation, then on the filter, and dried in the steam-closet. The compound had the composition expressed by the formula $\text{C}_{36}\text{H}_{40}\text{AgN}_7\text{O}_9$; it was therefore $\text{Ur} + \text{Ag} - \text{H}_2\text{O}$, or an atom of water had left upon the substitution of an atom of hydrogen by one of silver.

Theory of atoms.		Per cents.	Mean found.
C_{36}	432	52.55	52.41
H_{40}	40	4.86	5.15
N_7	98	11.92	12.47
O_9	144
Ag	108	13.13	13.38
<hr/>		822	

Half-Basic Silver Uromelanate, $\text{Ur} : \text{Ag} = 2 : 3$.—Uromelanine was dissolved in a minimum of ammonia, and the solution digested with an excess of uromelanine which remained undissolved. The solution was now boiled for a long time; as on cooling a slight deposit ensued the solution was filtered. It was then precipitated with silver nitrate, washed and dried at 100° to 105° . It yielded 18.57 per cent. of Ag, and contained, there-

fore, exactly two Ur upon three silver. Or it consists of one atom of neutral and one of basic salt.

$$\begin{array}{rcl} 2 \text{ uromelanine} - 3\text{H} & = & 1,463 \\ 3 \text{ silver} & & 324 \\ \hline & & 1,787 \end{array} = \left\{ \begin{array}{l} \text{Ur} + \text{Ag} \\ \text{Ur} + \left\{ \begin{array}{l} \text{Ag} \\ \text{Ag} \end{array} \right. \end{array} \right.$$

Two-thirds Basic Silver Uromelanate, Ur : Ag = 3 : 5.—Some uromelanine was dissolved in concentrated ammonia water, and after having been boiled down to one-half was precipitated with silver nitrate. The filtrate and first washing water were colourless, but the later washings became progressively darker. These dark filtrates, however, contained no trace of silver. The preparation contained 20·1 per cent. of Ag. It was therefore clear that the ammonia could not be sufficiently removed from a uromelanine solution by boiling down to one-half. A third of the same solution was treated with BaCl₂, and yielded the neutral baryum compound, as if the solution had been strongly alkaline. A second preparation was therefore made as follows:—The uromelanine was dissolved in ammonia and the solution was evaporated, not as in the first preparation only to one-half, but to dryness. The residue easily dissolved in water, leaving but an insignificant quantity of insoluble matter behind. This circumstance pointed to the presence of enclosed alkaline salt. The filtered fluid was treated with silver nitrate, and the flocculent precipitate washed on a filter. The first filtrate was colourless, the subsequent washings slightly coloured. Its analysis led to the following data:—

Pentargyric Triuromelanine.

	Atomic weights.	Required in 100.	Found mean.
C ₁₀₃	1,296	47·40	46·90
H ₁₂₄	124	4·53	4·77
Ag ₅	540	19·75	19·77
N ₂₁	294	10·75	10·36
O ₃₀	480	17·57	18·20
	<hr/> 2,734	<hr/> 100·00	<hr/> 100·00

This result by the following formula $\frac{2,734 - 540 + 5}{3} = 733$

leads to the atomic weight of uromelanine as also determined by other analyses. But this silver salt is the firmest basis for that theory, as it is very definite, and has been analysed repeatedly regarding its four directly determinable elements. The means found correspond in a remarkable manner with the requirements of theory.

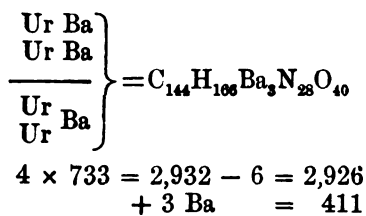
Half-Acid Baryum Uromelanate, $\text{Ur} : \text{Ba} = 5 : 2$.— Ur was dissolved in excess of concentrated ammonia, and precipitated by BaCl_2 . It was washed during more than a week with nearly 100 portions of water, before it became steady and the filtrates were free from Ba .

Theory of atoms.		In 100.	Found.
C_{180}	2,160	54.89	52.96
H_{211}	211	5.36	5.5
N_{35}	490	12.44	11.88
O_{80}	800
Ba_2	274	6.96	7.2
<hr/>			
3,935			

Neutral Baryum Uromelanate, $\text{Ur} : \text{Ba} = 2 : 1$.—A dilute strongly alkaline solution of uromelanine was treated with baryum chloride, the precipitate washed with water and dried. A second preparation was made from the same specimen by boiling its strongly alkaline solution down to one-half, and then precipitating it by BaCl_2 . During washing the coloured filtrates became darker, and the Ba ceased to be contained in them, before uromelanine. The precipitate was washed with alcohol, dried, and analysed.

Theory of atoms.		In 100.	Mean found.
C_{72}	864	53.96	...
H_{84}	84	5.24	...
N_{14}	196	12.24	11.3
O_{20}	320
Ba	137	8.55	8.34
<hr/>			
1,601			

Tribarytic Tetrauromelanine, $\text{Ur} : \text{Ba} = 4 : 3$.—The precipitation of this baryum salt has to be effected in a solution containing a minimum of ammonia, otherwise the gelatinous precipitate retains ammonia longer than the excess of chloride of baryum, and the alkali then decomposes a small quantity of the combination, so that the filtrates which at first are colourless become darker as the washing proceeds. The first washing is therefore best effected with water containing a little chloride of baryum, and ultimately the washing is completed with alcohol. The compound consists of one molecule of basic and one molecule of neutral uromelanate.

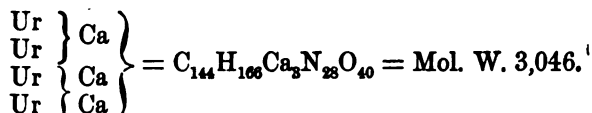


Molecular weight of compound = 3,337

This theory derives great support from the constitution of a calcium compound to be described lower down.

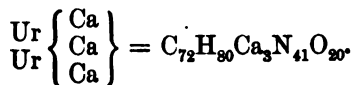
Half-Acid Calcium Uromelanate, Ur : Ca = 5 : 2.—The ammoniacal solution was made neutral by digesting it with excess of uromelanine, and after filtration boiling it, and filtering again from a little deposit which had formed. Ur 733 \times 5 = 3,665 + 2Ca = 80 - 4H = 3,741 requires 2.13 per cent. Ca, found 2.03 per cent. Ca.

Tricalcic Tetrauromelanine, Ur : Ca = 4 : 3.—In the preparation of this salt the same precautions have to be observed which have already been mentioned under uromelanine baryum. It has to be washed with water containing chloride of calcium, and ultimately the excess of chloride has to be removed by alcohol. The compound is exactly analogous to the tribarytic tetrauromelanine, and its formula is



Tricalcic Diuromelanine, or Hyperbasic Calcium Uromelanate, Ur : Ca = 2 : 3.—The strongly alkaline solution was precipitated with CaCl_2 and dried at 100°.

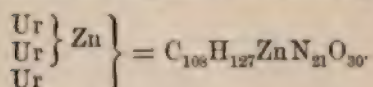
1,466 - 6 + 120 = 1,580, requires in 100° Ca 7.59, found mean 7.33.



Acid Zinc Uromelanate, or Monozinc Triuromelanine, Ur : Zn = 3 : 1.—A quantity of Ur was dissolved in ammonia and made neutral by boiling for 1½ hours. The vapour then did not give any fumes with the HCl glass rod. Sulphate of zinc was employed for the precipitation. Analysis yielded 2.82 per cent. Zn, which leads to the following theory:—

$$\begin{array}{rcl} 3 \text{ Ur} - 2 \text{ H} & = & 2,197 \\ 1 \text{ Zn} & = & 65 \end{array}$$

1 mol. of compound = 2,262 requiring 2.87 per cent Zn.

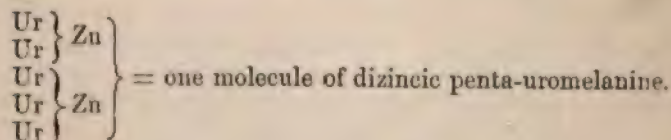


Normal Zinc Uromelanate, $\text{Ur} : \text{Zn} = 2 : 1$.—Some uromelanine was dissolved in concentrated ammonia, and after having been boiled to drive off the excess of ammonia, was precipitated with zinc sulphate. The filtrate and first washing water were colourless, but by progressive washing the water became darker. As these filtrates contained no zinc, the washing was arrested and the compound dried. The zinc was determined as oxide by combustion, and found to amount to 4.42 per cent. Zn. This leads to the formula $\text{C}_{72}\text{H}_{84}\text{ZnN}_{14}\text{O}_{20}$. M.W. = 1,529.

The solution employed in this experiment was one-third of a solution, the other third of which yielded the second preparation of normal or neutral baryum uromelanate, which contained 8.03 Ba. The last third of the solution by treatment with silver nitrate yielded not a normal but a two-thirds basic silver salt, or pentargyric triuromelanine with 20.11 per cent. of Ag or a trifle in excess of the theory.

Half-Acid Uromelanate of Zinc, $\text{Ur} : \text{Zn} = 5 : 2$.—A preparation was made by adding ZnSO_4 to a filtrate from uromelanate of ammonia which during evaporation had lost ammonia, and deposited a portion of its uromelanine in scales. Another preparation was obtained by treating the mother-liquors from urochrome preparation with lime, ultimately with ZnCl_2 to separate kreatinine. The kreatinine chloride of zinc deposit was washed, and then dissolved in boiling water. A gelatinous brown precipitate remained undissolved, and was found to be uromelanine zinc by analysis. The molecular weight of this salt is $2 \text{ Zn} = 130 + 5 \text{ Ur} - 4 \text{ H} = 3,661$, total = 3,791. This requires 3.42 per cent. Zn. Found 3.54 per cent.

It may be considered as a compound of two molecules of neutral zinc uromelanate and one molecule of uromelanine. Thus :



Half-Basic Uromelanate of Lead, $\text{Ur} : \text{Pb} = 3 : 2$.—A solution

of uromelanine from fresh urine in ammonia was made, so neutral that some uromelanine remained undissolved. To the clear filtrate neutral acetate of lead was added. The precipitation was perfect, the filtrate colourless. The precipitate was washed until the filtrates were free from lead.

Molecular weight of this compound :—

$$\begin{array}{rclcl}
 3 \text{ Ur} & - & 4 \text{ H} & + & 2 \text{ Pb} \\
 \hline
 733 \times 3 & - & 4 & + & 414 & = & 2,609. & \text{M. W.} \\
 \text{Pb required in 100} & & & & & = & 15.86. \\
 \text{,, found ,,} & & & & & = & 15.703. \\
 \left. \begin{array}{l} \text{Ur} \\ \text{Ur} \\ \text{Ur} \end{array} \right\} \left. \begin{array}{l} \text{Pb} \\ \text{Pb} \\ \text{Pb} \end{array} \right\} & = & \text{one molecule of diplumbic triuromelanine.}
 \end{array}$$

The Origin and Physiological and Pathological Significance of Uromelanine.

Uromelanine is not as such contained in urine, but is a product of the decomposition by putrefaction, or the influence of sulphuric acid and time, or sulphuric acid and heat of another substance contained in it. This original substance is urochrome, the colouring matter. When urochrome splits up into its constituents under the influence of putrefaction it does not immediately yield uromelanine, but a less oxydised substance of light yellow colour, which on exposure to oxygen quickly becomes brown; and during evaporation of the putrid urine, while exposed to air, assumes a perfectly black colour, and is in part precipitated.

The "melanine," which some Prague observers extracted from the urine of patients suffering from melanotic cancer, is nothing else than the uromelanine which can be obtained from all urine. But as they assert to have obtained the same substance from the tumours themselves, a remarkable inquiry is opened.

In his analysis of the pigment of the choroidea, Scherer had found results which it is interesting to compare with those yielded by uromelanine :—

Melanine of the Eye.	Ur.	Theory of Ur.
C . . . 58.28	57.21	58.93
H . . . 5.72	5.74	5.86
N . . . 13.77	13.88	13.36
O . . . 22.03

The composition of melanine is, therefore, very similar to that of Ur. as found, and more so to that calculated from its compounds.

Rosow, however, at a later period found in the pigment of the choroidea, Heintz in pigment from melanotic tumour—

Pigment of Choroidea.		Melanine of Tumour.	
C	. 54.0	C	. 53.44
H	. 5.8	H	. 4.02
N	. 10.1	N	. 7.1
O	. 30.	O	. 35.44
Ash	. 0.6		

As Rosow did not analyse a pure preparation, we cannot attribute the same value to his analyses as to those of Scherer.

Uromelanine has an atomic weight of 733. There are but very few organic substances which attain so high a number of carbon atoms as 36, and still fewer which combine with that number, besides hydrogen and oxygen, seven atoms of nitrogen. Uromelanine is a very stable body compared to any compound of similar atomic pretensions, and combines readily in a great variety of proportions with very different bases. Its derivatives of a substitutive or otherwise metamorphic quality promise to be very great in number, and invite the chemist to attentive study. But by far the greatest interest attaches to uromelanine as an animal matter, and particularly as that animal product which amongst all decomposition products of excretory substances of the animal economy occupies by its atomic weight and complicated constitution the highest place. It affords an imperturbable basis for the operations which animal chemistry will have to undertake in order to determine the nature, composition, and atomic weight of the colouring matter of urine. This latter must necessarily have a higher atomic weight than 733, and possess a constitution of singular complication and variety as regards the nuclei or radicals contained in it. Then if our ideas about the nature of excretory substances are correct in their application to urochrome no less than to uric acid, we are driven to the assumption that as uric acid is a derivate of albumen, so urochrome is a derivate of a constituent of the blood of much higher atomic complication than albumen, and as such we could claim only one material, namely, the most characteristic ingredient of the blood corpuscles, or hemato-crystalline, the crystallisable compound which may be split up into an albuminous body and into hematine. We thus may obtain, probably, a new means of estimating the effects of the febrile process upon the organ of oxygenation, the blood-disk, or its ally, the myochrome or red colouring matter of the muscles. But we also obtain by a direct process of reasoning a new insight into the chemical processes of life altogether. If uromelanine is of atomic weight 733, its precursor urochrome could not be a derivate of albumen with atomic weight 1,612, or

of fibrine with atomic weight 2,200, but would have to be derived from a compound of much higher chemical constitution. This could not be hematine, but solely hematocrystalline, to which we now begin to attribute the importance of being a chemical compound of about 13,000 atomic weight. Hitherto we had been taught that the animal was not a chemical machine with a synthetical tendency. It was believed to receive all its materials, its albumen, caseine, cerebral substances, in a ready-made condition from the plant; no doubt it organised them in the shape of tissues, but it was believed incapable of chemical synthesis of a high order. We shall now have to change these views completely. The highest atomic weight produced in the plant is about 2,200, the highest atomic weight produced in the animal is about 13,000. The complication of the material of the most developed chemical machine of the animal is six times greater than the most complicated material produced in the vegetable economy.

On the Quantity of Uromelanine Obtained by Chemolysis from Normal Urine.

Experiment 1.—The urine of a healthy man excreted during 24 hours (10 o'clock P.M. of Nov. 1 to 10 P.M. of Nov. 2), total quantity 2270 c.c., was evaporated rapidly over the free fire to a bulk of one-fifth, or 450 c.c., and after cooling and filtering, 5 c.c. of concentrated sulphuric acid were added. The mixture was allowed to stand in a warm place. Its colour became red, and no uric acid was deposited. On cooling it became turbid and deposited granules. These redissolved on warming, and thus repeatedly, by no means could crystals be obtained, and the matter could not be filtered, as it penetrated the filtering paper to a great extent. It was consequently evaporated on the steam-bath, allowed to stand for four days, and then 30 c.c. of sulphuric acid were added, and the mixture boiled in a flask attached to a condenser. After about 60 c.c. of distillate had been obtained the mixture deposited the products of urochrome. It was now diluted with its own bulk of warm water, and 22 c.c. of H_2SO_4 were again added, and redistillation commenced. After one hour's boiling another 10 c.c. of acid and a large quantity of water were added. A considerable precipitate formed, as on the first addition of water after boiling. On reheating a great froth rose, which had to be carefully managed until the particles which formed it had again coalesced by heat. The froth became more dangerous after every addition of water. This fluid was allowed to cool in a dilute state. Next day the precipitate was collected on a weighed filter and dried. The uromelanine, uropittine, and omicholine weighed .7165 grammes. The filtrate was again distilled down to the lowest point, and 10 c.c.

more acid added. A slight reaction ensued. The addition of the mixture to much water produced no immediate precipitate; but on standing a second deposit formed, which was filtered off.

The washed precipitate as weighed above was extracted with alcohol, and the residue collected on a weighed filter. The uromelanine obtained weighed 4273 grammes.

It was ascertained during this process that there would be some unavoidable loss, and consequently some inaccuracy if each day's product were treated separately. The products of all the following experiments were therefore first weighed by themselves, and afterwards united to those of the first, and extracted together.

Experiment 2.—Urine from 10 P.M. of November 2 to same hour of November 3, 1830 c.c. The experimental man had taken little food that day. The urine was mixed with 5 c.c. of H_2SO_4 and allowed to stand in an open dish during five days. Much decomposition took place, and therefore 62 c.c. more acid and a quantity of water were added, and the mixture distilled. This was repeated; ultimately water was added, and the mixture allowed to stand. It was then filtered and washed. The urochrome products weighed 4504 grammes. A trace was left on the paper.

Experiment 3.—Urine of November 3 to 4. 900 c.c. Evaporated, filtered, and 5 c.c. of HCl added. Remained light coloured, but deposited some urochrome products. 70 c.c. H_2SO_4 added and boiled for three hours. Precipitated with water and deposit collected on weighed filter. Urochrome products = 744 grammes.

Experiment 4.—Urine of November 4 to 5. 24 hours 1293 c.c. Evaporated 5 c.c. of HCl added, and allowed to stand some days. 70 c.c. of H_2SO_4 were added and the mixture boiled. The washed and dried precipitate of urochrome products weighed 5055 grammes.

Experiment 5.—Urine of November 5 to 6. 24 hours, 2080 c.c. Evaporated, filtered, and after standing by itself 7 days decanted from crystals 70 c.c. H_2SO_4 added and distilled. Urochrome products on filter = 6610 grammes.

Experiment 6.—Urine of November 6 to 7. 1160 c.c. (and 420 c.c. lost with a broken bottle). Evaporated and filtered. Boiled with 33 c.c. of H_2SO_4 17 c.c. more acid added to concentrated fluid, which effervesced with carbonic acid from the destroyed urea. On the addition of water much precipitate ensued, and the fluid seemed less coloured than when much acid was added. The urochrome products weighed = 3475 (calculated addition for loss 420 c.c. of urine = 1258 grm. of products).

Experiment 7.—November 7 to 8, 1840 c.c. Had been evapo-

rated to dryness and crystallisation, redissolved in little water, and filtered clear; remained clear on standing many days. 34 c.c. of H_2SO_4 added and boiled. Urochrome decomposed apparently very easily. Then 12 c.c. more acid and a large quantity of water were added. Urochrome products = 5870 grm.

Experiment 8.—November 8 to 9, 1610 c.c. Evaporated, filtered, 35 c.c. H_2SO_4 added and distilled for one hour; let stand for twenty-four hours; 22 c.c. H_2SO_4 and much water added, distilled to concentration. Urochrome products = 7895 grm.

Experiment 9.—November 9 to 10, 1280 c.c. (and estimated loss of 400 c.c.). Evaporated, filtered, stood two weeks, 50 c.c. H_2SO_4 added, and boiled twice. Urochrome products = 3730 grm. Calculated products for loss 400 = 1165 grm. Total excretion 4895 grm.

Experiment 10.—November 10 to 11, 1470 c.c. evaporated. Was partially ammoniacal, 40 c.c. of H_2SO_4 added and twice boiled. Urochrome products = 4110 grm.

Experiment 11.—November 11 to 12, 1680 c.c. Evaporated and filtered. Has stood long and become thoroughly ammoniacal. The urochrome, however, did not seem to be decomposed yet, as on addition of H_2SO_4 only frothing and no precipitate ensued. Added 50 c.c. of acid and boiled for $1\frac{1}{2}$ hour. Total products = 2340 grm.

The following is a tabular summary of the above experiments:—

No. of Experiment.	C.C. in 24 Hours.	Total Products.	Uromelanine.	Omicholine and Uropit. time. Omicholic Acid.
1	2270	7165	4273	2892
2	1833	4504	2572	1932
3	900	7440	4251	3189
4	1293	5055	2888	2167
5	2080	6610	3777	2833
6	1580*	4733	2704	2029
7	1840	5870	3354	2516
8	1610	7895	4511	3384
9	1680†	4895	2797	2098
10	1470	4110	2348	1762
11	1680	2340	1337	1003
Total of days	18,236	60617	34812	25805
Mean per day	1657	5510	3164	2346

* Note to Experiment 6, loss of 420 c.c. added.

† Note to Experiment 9, estimated loss of 400 c.c. added.

More than half a grm. of urochrome products is therefore obtained from the average daily urine of a healthy man, and of these 551 grm. four seventh parts, i.e., 3164 grm. are uromelanine, the remaining 2346 are uropittine, omicholine, and omicholic acid.

Special Identification of the Uromelanine Obtained in these Experiments.

The uromelanine obtained as above was dissolved in dilute ammonia and evaporated slowly on the water-bath to dryness. On addition of water much uromelanine remained in the pseudo-crystalline insoluble form, another portion dissolved. This solution was precipitated with silver nitrate, and dried at 110° to 120° during two days until constant. 6564 grm. after careful combustion left 0830 grm. Ag, or 12.64 per cent. $C_{30}H_{40}AgN_7O_9$ requires 13.13 per cent. Ag. This proves the product to have been very pure uromelanine.

Experiment 12.—The whole amount of urine passed in twenty-four hours, amounting to 2072 c.c., was evaporated to a syrupy consistency, and then some dilute sulphuric acid added to it. After twenty-four hours' standing the precipitate was separated, and found to consist of uric and hippuric acid, coloured brown by a little colouring matter. The filtrate was mixed with a little more sulphuric acid and distilled on the sand-bath. The first portion of distillate had a penetrating odour, and was yellow; over night it became darker. The later distillates were almost colourless, and remained unaltered. The fluid in the retort was filtered from the formed deposit, the latter washed, and extracted with alcohol. What remained insoluble, uromelanine, was dried at 105°, and found to amount to 0.7315 grm. The alcoholic extract, containing omicholine, omicholic acid, and uropittine, after evaporation of the alcohol, amounted to 0.3472 grm.

It is remarkable that the quantity of uromelanine obtained from a day's urine is about equal to that of the uric acid excreted on an average under similar conditions.

Uromelanine, &c., in a Case of Tropical Fever.

A gentleman, a coffee planter from the south of India, was obliged by unceasing attacks of fever to return to England. He arrived emaciated, with a yellow coloured skin peculiar to the subjects of tropical fever. His tongue was much furred; the liver was so greatly enlarged that the probability of its containing an abscess had been suggested. The urine was of a deep red colour, and deposited urates. The urine from two days was subjected to the chemolytic process described in the foregoing.

During boiling of the products in alcohol a small quantity was lost by bumping, the quantities found by weight are therefore only approximatively correct.

Uromelanine found,	.	.	0.2915 grammes.
or per 24 hours,	.	.	0.14575 "
Uropittine and omicholine,	.	.	0.1242 "
or per 24 hours,	.	.	0.0621 "

The products soluble in alcohol stand therefore to the uromelanine in the same relation of quantity as in the healthy urine. The total quantity of products was certainly less than from healthy urine, although the actual amount cannot, owing to the accidental loss, be accurately stated.

This urine yielded no uric acid whatever, and the filtrate from the uromelanine was unusually dark, as if it contained an abnormal colouring matter in solution.

*Note on the Effect of Iodine upon the Mother-Liquors of the
Chemolytic Products.*

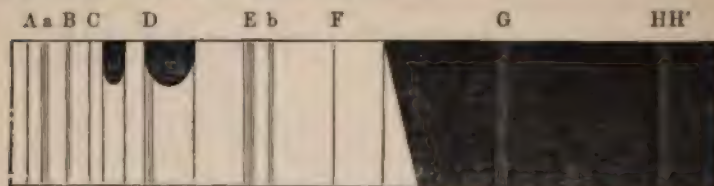
When iodine dissolved in iodide was added to the acid liquids obtained as above, representing 11 days' urine, a copious precipitate ensued. The iodine was added until no further reaction ensued. The precipitate was viscous. Washed and dried it weighed 85 grammes, being 7.7 grammes for every single day. This compound has yet to be examined.

Paramelanine.

As in spectroscopic analysis of inorganic matters, light shoots up here and there for an instant, marking the presence of a minute amount of some matter or other, so in general analysis a few collateral products are met with, which indicate their own existence, but at the same time a genetic coherence of the matters under investigation. While uromelanine preserves no reminiscence in its optical characters of the hematine to which it has such particular similarity by its stability and high atomic weight, there is accompanying it a small amount of a substance, which, when treated with sulphuric acid, yields a spectrum similar to that of cruentine.

This body I term paramelanine. It was obtained in the following manner:—Uromelanine, after separation from the products soluble in alcohol, was dissolved in potash and reprecipitated by sulphuric acid. It was washed with water, lastly with alcohol. These alcoholic solutions had stood a long time and deposited a black matter. This was found to have become in-

soluble in ammonia. Dissolved in concentrated sulphuric acid it showed a spectrum with two bands.



Spectrum of Sulphate of Paramelanine.

The two bands are therefore of the same breadth as those of cruentine sulphate, but they are situated more towards the violet. On addition of water the solution remains clear, and the dilute liquor retains the bands. But the ammoniacal solution exhibits no bands, and thus differs greatly from that of cruentine.

Omicholine and Omicholic Acid.

Mode of Obtaining.—The resinous matter obtained by filtration from the acid mother-liquor may be dried, and extracted at once with ether to obtain these substances. Uromelanine and uropittine remain insoluble in ether; uropittine is then extracted by means of alcohol. This succession is probably preferable to the one employed in the following process :—

The mixture of substances which alcohol extracts from the chemolytic products of urochrome (which are insoluble in the acid mother-liquor and in water) is evaporated to a small bulk, and then poured into water. The precipitate is collected on a filter and washed until all traces of impurities have disappeared from the filtrates. The matter is now allowed to dry spontaneously, or in vacuo over sulphuric acid (not by heat, as the matter fuses and penetrates into or through the paper), and then in a flask extracted with ether. This operation is very difficult, as the matter cannot be powdered; and in the ether immediately settles in the form of smeary hard lumps. However, after weeks of continued extraction all resinous matter has passed into the ether, and a pulverulent matter, *uropittine* (perhaps *urorubine*), and some uromelanine, remain undissolved. The ethereal solution is of a bright port-wine red colour, and peculiar, independently of the ether, penetrating odour. When the ether is allowed to evaporate spontaneously, or distilled off, a red syrup remains, which may become hard, but never shows any signs of crystallisation. It was this body which I had described as omicholic acid in the Hastings Prize Essay. The following will show that it is a mixture of two closely related bodies, which can, however, be separated to some extent, though imperfectly.

Mode of Separating Omicholine from Omicholic Acid.—The

resin is treated with concentrated liquor ammoniæ and warmed. A portion dissolves, while another portion settles as a thick brown oily liquid. The alkaline solution is decanted and allowed to stand when it will deposit more of the oily matter. (This portion is rejected, as being probably a mixture of omicholine and omicholic acid, which it is impossible entirely to separate). When the alkaline solution in a covered vessel does not deposit any more oily matter, it is considered free from omicholine, and to contain only omicholic acid dissolved with ammonia, and some uropittine. The deposit is omicholine.

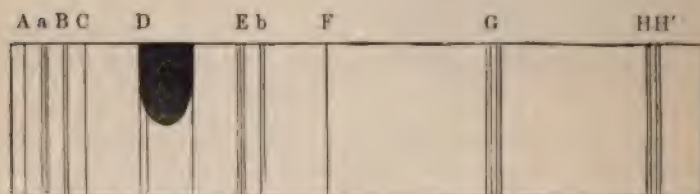
Purification of Omicholic Acid.—To the watery ammonia solution some BaCl_2 is given, which precipitates most of the uropittine, and any trace of uromelanine which may be present. (The baryum salt in one case gave 20 per cent. Ba.) The filtrate is acidified with hydrochloric acid, which precipitates all omicholic acid as resin. It is washed with cold water. If no uropittine be discovered by testing, sulphuric acid is added to the ammonia solution. In this case a precipitate ensues, but much omicholic acid remains in solution. On evaporation of the acid liquid it is deposited in drops. All omicholic acid is easily taken up by ether from the acid watery liquid or mixture.

Purification of Omicholine.—The deposited omicholine is mostly free from uropittine and uromelanine, which easily dissolve in the watery ammonia; but it must be well washed with water, and a trace of acid, before it is pure.

Ultimate Purification of Omicholine and Omicholic Acid.—Each of these bodies is dissolved in absolute alcohol, and to this solution six volumes of absolute ether are added. Any precipitate is impurity, either uropittine or other matter. When the mixture remains clear the matter dissolved in it, provided it has been treated as above stated, must be considered as pure as in the present state of our knowledge it can be obtained.

Chemical Properties of Omicholine.—It is semi-fluid to resinous, becoming harder by keeping. It has a red colour and strong peculiar odour. It is little soluble, or insoluble in concentrated caustic ammonia, and does not combine with baryum salts. It is soluble in caustic potash, and again precipitated by sulphuric acid. It is a little soluble in cold water on standing, a little more soluble in boiling water, with a yellow colour; the solution becomes turbid on cooling. The cold watery solution becomes turbid on addition of a little sulphuric acid; on heating it clears up again. The watery solution, hot or cold, gives a precipitate with (1) sulphuric acid and iodine dissolved in iodide; (2) with mercury oxyde nitrate, yellow-white; (3) with the same and subnitrite or nitrite of suboxyde, a red reaction like tyrosine. All watery solutions are strongly fluorescent. Silver nitrate gives no immediate precipitate in the hot saturated watery solution,

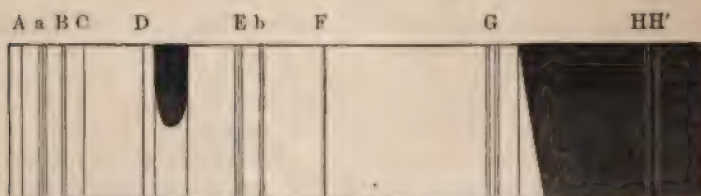
but on standing a precipitate is formed. Its spectral phenomena are most remarkable. The ether solution is of a ruby-red colour, but fluoresces green in the cone of the sunlight. In the spectroscope it shows an absorption band in green. Near to it in green there is a shading.



Spectrum of Omicholine.

The red and yellow are very brilliant; the rest of the spectrum after green has a violet hue, without any blue.

Physical and Chemical Properties of Omicholic Acid.—This acid is of a red colour, resinous, fusing when heated, and giving out the aromatic strong odour reminding of castoreum. It is little soluble in water, more in ether, best in absolute alcohol. It dissolves in concentrated watery ammonia, and more easily in caustic potash. The ether solution, which is ruby-red, shows an absorption band in green.



Spectrum of Omicholic Acid.

The blue part of the spectrum is coloured violet, green shaded. Omicholic acid in chloroform has the same spectrum; but as the solution can be obtained more concentrated than the ether solution, the violet, blue, and nearly the whole of the green part of the spectrum are cut off entirely immediately to the right of the absorption band. The ammoniacal solution of omicholic acid has no bands in the spectrum. Omicholic acid is red, and fluoresces green in the sunlight cone, or that of the electrical lamp, but its phenomena differ slightly from those of omicholine.

Elementary Composition of several Specimens of Omicholine and Omicholic Acid.

Omicholine, I. a.

	In 100.	Quotient by At. W.	Quotient by N = 1.
C . . .	64.67	5.3891	23.5
H . . .	10.04	10.0400	43.9
N . . .	3.20	0.2285	1.
O . . .	22.09	1.3806	6.04
Formula $C_{24}H_{44}NO_6$.			

Omicholic Acid, I. b.

	In 100.	Quot. by At. W.	Quot. by N = 1.
C . . .	63.65	5.304	15.92
H . . .	8.14	8.140	24.44
N . . .	4.67	0.333	1.
O . . .	23.54	1.471	4.41
Formula $C_{16}H_{24}NO_4$.			

Omicholine, II. a.

	In 100.	Quot. by At. W.	Quot. by N = 1.
C . . .	69.64	5.8033	22.
H . . .	10.14	10.1400	38.5
N . . .	3.68	0.2628	1.
O . . .	16.54	1.0337	3.9
Formula $C_{22}H_{38}NO_4$.			

Omicholic Acid, II. b.

	In 100.	Quot. by At. W.	Quot. by N = 1.
C . . .	63.17	5.264	15.08
H . . .	7.58	7.580	21.71
N . . .	4.89	0.349	1.
O . . .	24.36	1.522	4.36
Formula $C_{16}H_{21}NO_4$.			

Omicholine, III. a.

	In 100.	Quot. by At. W.	Quot. by N = 1.
C . . .	66.20	5.516	21.80
H . . .	8.14	8.140	32.17
N . . .	3.55	0.253	1.
O . . .	22.11	1.384	5.46
Formula = $C_{22}H_{22}NO_5$.			

Omicholic Acid, III. b.

	In 100.	Quot. by At. W.	Quot. by N.
C . . .	64.89	5.4075	14.70
H . . .	8.335	8.3350	22.66
N . . .	5.15	0.3678	1.00
O . . .	21.63	1.3518	3.67

Formula $C_{15}H_{23}NO_3$.

The preparation III. *a* and III. *b* had been boiled with sulphuric acid in the urinary extract, while I. *a*, I. *b*, and II. *a*, II. *b*, had been obtained by the influence of sulphuric acid upon the urine extract without boiling.

Synopsis of Formulæ of Omicholine and Omicholic Acid according to Preparations.

{ I. <i>a</i> .	$C_{24}H_{44}NO_6$
{ I. <i>b</i> .	$C_{16}H_{24}NO_4$
{ II. <i>a</i> .	$C_{22}H_{38}NO_4$
{ II. <i>b</i> .	$C_{15}H_{21}NO_4$
{ III. <i>a</i> .	$C_{22}H_{32}NO_5$
{ III. <i>b</i> .	$C_{15}H_{23}NO_3$

Synopsis and Mean of Formulæ of Omicholine.

I. <i>a</i> .	$C_{24}H_{44}NO_6$
II. <i>a</i> .	$C_{22}H_{38}NO_4$
III. <i>a</i> .	$C_{22}H_{32}NO_5$
Mean formula of } omicholine . }	$C_{22}H_{38}NO_5$

Synopsis and Mean of Formulæ of Omicholic Acid.

I. <i>b</i> .	$C_{16}H_{24}NO_4$
II. <i>b</i> .	$C_{15}H_{21}NO_4$
III. <i>b</i> .	$C_{15}H_{23}NO_3$
Mean formula of } omicholic acid }	$C_{15}H_{22}NO_4$

These bodies are evidently well-defined different entities, although they have not yet been obtained in a pure state. They differ from each other, but cannot yet perhaps be absolutely separated from each other. On the other hand, they have so many properties in common, that the one may possibly be derived from the other, or that both may have a common origin. Their molecular weight has not yet been determined, as no compound appeared definite enough for that purpose.

The importance of these bodies in pathology may be inferred from the fact that they are capable of forming in the human body in certain forms of kidney disease. The breath and the exhalation of the skin in such cases smell strongly of omicholine and omicholic acid. Their nauseous and emetic properties, al-

ready observed by Proust, may perhaps contribute to the explanation of that peculiar vomiting which occurs in cases of chronic kidney disease, in which dropsy and œdema have naturally, or by the constant use of the Turkish baths, ceased to be factors of the pathic process.

Those who would study these matters further should extract the materials from several thousand gallons of urine in order to obtain quantity sufficient for all purposes. The quantity of omicholine and omicholic acid which can be obtained from lesser quantities of urine is indeed not small; but of the mixed resin obtained so much is lost in the various processes of purification, that what remains is the lesser portion, and insufficient for that varied analysis and testing which uncrystallisable and uncombinable substances more than any others require.

Uropittine, Metauropittine, Urorubine.

When the mixture of substances obtained by chemolysis with sulphuric acid from extract of urine is extracted with ether, omicholic acid, and omicholine pass into solution. Alcohol next extracts from the part insoluble in ether a considerable quantity of what I have termed *uropittine*, mixed with a small quantity of matters very similar to it in chemical properties, but differing slightly in composition, and which may be termed *metauropittine* and *urorubine*. I have not yet effected a separation of these substances, but give in the following the results of some experiments in that direction, and the results of some analyses of the free substance as well as of some of its combinations.

I have endeavoured to free uropittine from matters soluble in water by pouring the concentrated alcohol solution (filtered from some uromelanine, which when freshly formed is a little more soluble in alcohol than after it has been isolated for some time) in water; it is thereby precipitated, and the uropittine may be collected on a filter and washed; much matter, however, is lost in the mother-liquor.

I have examined and analysed either in the free or combined state the following preparations:—

I. This specimen of uropittine was dissolved in ammonia and the alkaline solution treated with barytic chloride. The ensuing precipitate was washed and dried at 110°. It contained 20·21 per cent. Ba.

A portion of the ammoniacal solution was evaporated to dryness. Of the residue a small part only dissolved in water, the greater part remained undissolved. Silver nitrate was added, and the mixture boiled. The precipitate was washed on the filter until the filtrates were free from silver and colourless. The dry compound contained 21·39 per cent. Ag. and 12·27 per cent. N.

II. This substance was precipitated by ether from the solution

in absolute alcohol of the mixed urinary resins. It was dried at 100°, and did not become soft.

Synopsis of Analyses.

	1.	2.	3.	4.	Mean.
C . . .	60.30	59.90	60.10
H . . .	6.29	7.04	6.66
N	10.44	10.50	10.47
O	22.77
					<hr/> 100.00

III. Uropittine precipitated by ether was dissolved in ammonia, and to the solution some more uropittine was added in order to ensure its neutrality; thereupon it was precipitated by silver nitrate. After having been boiled, a proceeding which seemed necessary to cause the immensely voluminous precipitate to contract, it was collected on a filter. It appeared of a dark green colour, while the mother-liquor was slightly yellow. The washing liquors were of a darker colour than the mother-liquor, and fluoresced strongly.

Synopsis of Analyses.

	1.	2.	3.	4.	Mean.
C	36.52	...	36.52
H	3.99	...	3.99
Ag . . .	38.67	38.75	38.71
N	6.94	6.94
O	13.84
					<hr/> 100.00

Another quantity of the same preparation precipitated by ether from the alcoholic solution of mixed resins was dissolved in ammonia, and precipitated by hydrochloric acid. It was then again dissolved in a few drops of ammonia, and the solution made as neutral as possible by digesting it with an undissolved excess of uropittine. The filtered solution was precipitated by silver nitrate, and the precipitated silver uropittate was collected on a filter and washed. The mother-liquor and the filtrates were colourless. The precipitate was dried at 110°.

Synopsis of Analyses.

	1.	2.	3.	4.	5.	Mean.
C	37.95	37.95
H	4.29	4.29
Ag . . .	35.81	35.17	35.49
N	6.59	6.39	6.49
O	15.78
						<hr/> 100.00

These data show that the silver-salt must not be boiled, as unlike uromelanine, it is decomposed by heat.

It was attempted to produce a baryum salt from a portion of this specimen. Its solution in ammonia was precipitated by barytic chloride. The mother-liquor after filtration was dark coloured, but the washing water became constantly lighter, until it appeared only slightly yellowish at last. Although 0.5 gm. of uropittine had been dissolved, only 0.1605 gm. of baryum salt were obtained. It contained 7.10 per cent. Ba. Uropittine baryum is therefore very soluble in water.

IV. It was attempted to produce a neutral solution of this preparation by evaporation of its ammonia solution. The addition of CaCl_2 produced a compound which contained mean 1.78 per cent. Ca and 12.16 per cent. N.

V. This specimen was dissolved in a slight excess of ammonia, precipitated by BaCl_2 , and dried at 110° . It contained 21.77 per cent Ba.

Another portion of the same specimen was dissolved in ammonia, and the solution evaporated to dryness. Of the residue only a small part dissolved in water, the rest remained insoluble. Silver nitrate was added and the mixture boiled. The precipitate was washed upon the filter until the filtrates were colourless and free from silver. Dried at 110° the compound gave 27.14 per cent. of Ag.

VI. Another specimen of uropittine had been precipitated by ether from an alcoholic solution. It was dissolved in ammonia, evaporated and precipitated by silver nitrate. The washed precipitate, which had not been heated, was dried in vacuo over sulphuric acid, light being carefully excluded. It formed a glistening, blackish-violet-brown mass, and contained 27.0 per cent. of Ag.

VII. The uropittine described in the Hastings Prize Essay had yielded on analysis the

	Mean in 100 parts.	Quot. by At. W.	Quot. by N = 1.
C . . .	55.25	4.604	5.32
H . . .	5.57	5.570	6.44
N . . .	12.10	0.864	1.
O . . .	27.08	1.687	1.952

Metauropittine.

This body resembles uropittine in composition, but differs by being more easily soluble in alcohol. It does not fuse in heat. After extraction of matters soluble in ether alcohol easily dissolved this matter. It was precipitated by water, washed and dried at 100°C . It was much less in quantity than urorubine, to be described below.

Mean of analyses:—C=54.5; H=6.25.

Urorubine.

It had been separated from the uropittine described and analysed in the Hastings Prize Essay. It was easily soluble in cold absolute alcohol, and stood for three months in it to deposit body less soluble (Uropittine). It had then been precipitated by water, filtered and dried in vacuo. It was very hygroscopic, and after drying at 100° , when it did not fuse, always gained from two to three milligrammes under the dryer. After three days of drying the last weighing was assumed as practically correct.

Three combustions agreeing well together gave means— $C=65.27$ per cent.; $H=6.86$ per cent.; $N=11.46$ per cent. The body contains more carbon than either uromelanine or uropittine.

It is evident that from these data no formula or theory of uropittine can be constructed. The body is nevertheless apparently very definite, and produced not in small quantity, as I have obtained several hundred grammes of it in the course of my operations. It is probably oxydisable, and changes many of its properties on keeping. Thus it has a distinct spectrum (absorption in green) when freshly obtained, but on keeping loses all specific absorption.

I look upon these and like analyses as merely tentative. When the same process applied to the same preparation yields the same compound, this constitutes a symptom in favour of the supposition that the compound is definite, i.e., in atomic proportions. By producing a great many such compounds under varying conditions, those which conform to atomic laws are easily found out by their repetition. If instances remain isolated, their accidental and non-specific nature is proved. I consider this proceeding one of the few which in the present state of our knowledge of these matters can be applied for the obtaining of the precise information which is so urgently required.

CHAPTER XIX.

ACETIC AND FORMIC ACID.

PRELIMINARY NOTES.

PROUST was the first to obtain acetic acid, or as he termed it "vinegar," by the decomposition of extract of urine. It was subsequently again obtained by Liebig from putrid urine, and believed by him to be a product of decomposition of the colouring matters. He did not obtain it from fresh urine, and believed that the other products of the chemolysis of urochrome, the pitchy resins first described by Proust, could not be obtained from fresh urine, but were products of putrefaction. In a previous chapter I have enumerated the products of the chemolysis of urochrome, and amongst the volatile products I have stated the principal ones to be acetic, formic, and small quantities of higher acids. Formic acid had been repeatedly found to be an ingredient of human urine, but it had been declared an accidental product of the intentional ingestion into the stomach of certain substances which by decomposition in the economy yielded that acid. Moreover, its presence had only been assumed on the basis of a few reactions which did not exclude phenol (which yielded similar reactions), it had not been found to be accompanied by acetic acid, which made the statement open to objection, and it had never been identified by its cardinal tests.

Modes of Obtaining Formic and Acetic Acid from Urine.

These methods were first described by me in the Hastings Prize Essay, and may here be quoted :—

(a.) *From Fresh Urine*—The urine is evaporated over the free fire to one-tenth, and filtered from the phosphates, urates, and gypsum. It is then slowly evaporated on the sand-bath until a pellicle of urates forms. After cooling and filtering, it is evaporated on the water-bath to a syrup, and allowed to cool slowly with the water-bath, to effect a good crystallisation of chloride of sodium, urea, and other salts. The decanted syrup, if necessary, mixed with a little water, is treated with calcined magnesia, until alkaline, and until a filtered sample, treated with acetic

acid and chloride of iron, does not give any immediate precipitate. The extract is then filtered, put into a capacious beaker, and mixed with concentrated sulphuric acid, added, drop by drop, while the fluid is being agitated. A little uromelanine and some gypsum are precipitated in flocks. After filtration the fluid is diluted with water, and distilled in a capacious retort. When the fluid has been reduced to one half, the black resin will be seen adhering to the sides of the glass and to the platinum, which it is well to put into the retort to prevent bumping. The boiling is now interrupted, and the fluid allowed to cool. Fluid and resin are separated by decantation or filtration. The particles of resin are united by fusion in hot water. They are then washed, dried, and the resin is extracted from the black matter by solution in alcohol. The distillates, containing the volatile acids, are treated as stated lower down.

(b.) *From Putrid Urine.*—Putrid urine is treated with a little lime in powder, or sawdust, and filtered. The dark brown filtrate is evaporated in an open dish over the free fire. Although it soon assumes a strongly acid reaction, nothing but ammonia passes away. All froth which rises during the evaporation is carefully skimmed off. When black particles begin to appear on the surface it is allowed to cool, filtered, put into a retort, mixed with dilute sulphuric acid, and distilled. A mixture of hydrochloric, benzoic, acetic, and another acid passes over, together with a stinking matter, which deposits in flakes when the distillate is left to stand. The residue in the retort soon deposits the resin as a soft tar on the surface of the fluid, the sides of the vessel, and the platinum, put into the fluid for safe boiling. The resin is separated mechanically and by the filter, washed, and separated into its constituents by alcohol. The uropittine and uromelanine thus obtained present the same essential properties as those obtained from fresh urine.

Treatment of the Distillates.—Any solid benzoic acid (which occurs only in distillates from putrid urine, the distillates from fresh urine have all benzoic acid in solution) is filtered off. The fluid is then neutralised with powdery sodium carbonate and concentrated on steam. When it becomes red and emits a powerful aromatic odour, it is allowed to cool and extracted with ether as long as this reagent extracts any of the essential volatile oil which yields the tyrosine reaction with mercuric nitrate on boiling. The solution of salts is then further concentrated to near crystallisation, and decomposed with an excess of sulphuric acid. The benzoic acid collects as a thick magma on the top of the fluid, and is filtered off. The liquid is mixed with water and distilled. The distillate is now already much purer, and is again neutralised, &c., and distilled once more. A pure solution of acids

is now obtained which yields the reaction of both formic and acetic acid, and smells of butyric and caproic acid as well. Boiled with lead carbonate they yield lead salts, which crystallise sometimes, particularly with the help of a little ether, at other times remain as a colourless, transparent, thick and solid, yet somewhat viscid mass. By no means, however varied, could pure crystals be obtained from the watery solution.

Extraction of Neutral Lead Acetate by means of Alcohol.—The watery solution of the first deposit from water was poured into alcohol. The mixture after standing some days deposited a large bulk of fine acicular crystals. They were isolated and allowed to drain on paper. When dry they contained (1.61 of moisture and) water of crystallisation, as follows:—

(1.) 2.5725 grm. dried at 130° , fused, and frothed up, and smelled faintly of vinegar. After many days' drying they lost 0.4052 grm. of aq., leaving 2.1573 grm. of dry salt. Consequently the total loss was 15.81 per cent., from which deduct the theoretical loss of $3\text{H}_2\text{O} = 14.2$ per cent., leaves a slight excess of moisture, as stated.

(2.) 2.1573 grm. of the dry salt were treated with H_2SO_4 , and then cautiously heated to redness, acid being once more added during an interval of the ignition. There remained 2.005 PbSO_4 , while theory would require 2.0102. The dry salt therefore contains 63.66 per cent. of Pb, i.e., the theoretical quantity required by neutral acetate.

Extraction of Half-Basic Lead Acetate from the Mixture of Lead Salts, $(2(\text{C}_2\text{H}_3\text{PbO}_4) + \text{PbO})$.—This salt has hitherto been obtained in chemical inquiries concerning acetic acid: (a) by heating the neutral salt to 280° , and keeping it at that temperature until the fused salt sets again; (b) by digesting the watery solution of two molecules of the neutral salt with one molecule of powdered lead oxide free from carbonic acid, until solution has taken place, and evaporating. The salt has an alkaline reaction. In the present research, however, this salt was obtained as follows:—The acetic acid (containing formic) was treated with lead carbonate and boiling until saturated, and the filtrate evaporated. At a certain point it crystallised entirely. After resolution a small amount of salt crystallised first, and was separated and purified by recrystallisation. The saturated solution was now poured into a large amount of alcohol. Crystals deposited over night which were short prismatic needles of glassy lustre, and on analysis gave the following results:—At 190° they lost a trifling amount of moisture, and remained constant; they were consequently anhydrous.

(1), .8693 grm. on combustion left .654 grm. of residue, being lead oxyde = .434 grm. equal to .4028 PbO , and .22 metallic lead, total Pb = .6228 grm. or 71.60 per cent. (2),

1.1805 grm. left .8766 grm. residue, being .5456 PbO, equal to .5064 Pb, and .331 Pb, total Pb = .8374 or 70.93 per cent.

Mean of these analyses = 71.26 per cent. Pb.

Required by the above formula 71.37 per cent.

Schindler obtained a hydrated crystallised salt of this compound, which contained two atoms of water. He poured the saturated watery solution into an equal or double amount of alcohol (strength not stated), when the salt was deposited in pearly scales. At 90° they lost 2 per cent. of water, fused, and on cooling formed a colourless gum. This when heated further was transformed into a white mass, losing more water. These forms of pearly scales, colourless gum, and white mass were also obtained by heating the solution of the salt from urine on the water-bath and letting stand.

The circumstance that the crystals in the foregoing experiment were anhydrous, admits of explanation by the fact that a large volume of strong alcohol was employed in their separation. They moreover admit of no theory if considered to have contained any formiate.

But the *third* and *fourth* crystallisations were evident mixtures of neutral acetate and formiate; the latter crystallised in little opaque granular groups, while the acetate crystallised in brilliant crystals. The third crystallisation contained little, the fourth much formiate. The *fifth* crystallisation had a remarkably homogeneous appearance, and was analysed.

(1.) 1.1230 grm. yielded 1.1050 grm. PbSO_4 = 67.22 per cent. Pb.

(2.) 1.2915 grm. yielded 1.280 grm. PbSO_4 = 67.67 per cent. Pb.

Mean = 67.44 per cent. Pb.

In a mixture yielding the half-basic salt, the quarter-basic could also be formed, which requires 76.95 per cent. Pb. But the fact that the third and fourth crystallisations contained increasing quantities of formiate, made it probable that the fifth also contained formiate, although in appearance it was quite homogeneous. This was indeed established by a special examination, which yielded the reduction tests, and in one experiment with sulphuric acid so much carbonic acid and carbonic oxyde was obtained, that the conclusion was unavoidable that the mixture of crystals contained at least one-half by weight of formiate. In the sixth crystallisation, which also appeared quite uniform, the following relations were found:—

4.1580 grm. yielded 4.1240 PbSO_4 equal to 67.74 per cent. Pb.

Consequently the lead had increased a little; the salt contained a little more formiate, which requires 69.6 per cent. Pb; but even at the end no pure formiate could be obtained. The last mother-liquors contained small quantities of acid with less than the proportion of lead in acetate. In short, in this instance

the process of fractional crystallisation failed entirely in yielding any pure product after the preponderance of acetate had ceased, and even the employment of alcohol did not effect that neat separation of formiate (insoluble) from acetate (soluble in alcohol) which is advised in handbooks as if it were a fact; for the acetate was found to hold the formiate in solution, even in alcohol, or to fall with it from the more concentrated solution.

Baryum Salts of the Volatile Acids from Urine.—The lead salts having failed to afford the means of a neat separation of the acids, a new quantity of the acids was prepared and transformed into baryum salts by boiling with baryum carbonate. The solution was evaporated, and when in a syrupy state was put aside for crystallisation. Crystalline crusts were slowly deposited and removed. These first crystals were not analysed, but the next crystals (2d crystals) were perfectly colourless and homogeneous, and were analysed.

(1.) .3258 grm. gave .2992 grm. BaSO_4 , equal to 53.99 per cent. Ba.

(2.) .3998 grm. gave 0.3680 grm. BaSO_4 , equal to 54.12 per cent. Ba.

Theory for acetate, 53.72 per cent. Ba. Mean found, 54.05. This crystallisation, therefore, consisted of pure acetate. It yielded all cardinal reactions of acetic acid with precision, and was free from formic.

The mother-liquor now was allowed to stand, and formed a crust on its surface. Underneath that crust large beautiful crystals of rhombohedric shape, the obtuse corners cut off by a hemitropic (round principal axis) rhombohedron of greater elongation, were formed. They were of glass-like lustre and transparency. Some were detached entire and analysed separately.

(1.) .7712 grm. lost at 110° .1010 grm. aq. or 13.09 per cent. From this it might have been supposed that the crystals were a new hydrate of baryum acetate, of the formula $\text{C}_4\text{H}_6\text{BaO}_4 + \text{H}_2\text{O}$, At. W. 291, requiring 12.37 per cent. of aq., but

(2.) The .6702 of dry salt yielded .6362 grm. BaSO_4 , equal to .3736 Ba or 55.74 per cent. The theory of the acetate requires 53.72 per cent. The dihydrated baryum acetate should by direct combustion, without previous drying, yield 47.07 per cent. Ba. but

(3.) .7878 grm. (which frothed up on heating suddenly) left .66 BaSO_4 , equal to 49.25 per cent. Ba.

The crystals therefore contain, both in the anhydrous and dihydrated state, 2 per cent. Ba more than corresponds to acetate. The ordinary monohydrate of baryum acetate, $\text{C}_4\text{H}_6\text{BaO}_4 + \text{H}_2\text{O}$, contains 6.59 per cent. aq., and 50.18 per cent. Ba. It was therefore probable that these crystals were

not acetate, or not acetate only, and on examination it was found that they contained a considerable amount of formiate. The amount can be appreciated by putting the figures for Ba in acetate, crystals and formiate side by side.

Acetate requires	Crystals contain	Formiate requires
Ba 53.72 per cent.	Ba 55.74 per cent.	Ba 60.35 per cent.

The crystals correspond to a mixture of nine molecules of acetate with four of formiate, which requires 55.76 per cent. Ba. The form and stoichiometric relation of the water are probably an imitation of a new baryum acetate dihydrate. *They show that baryum acetate and baryum formiate are isomorphous, and cannot be separated from each other by crystallisation in mixtures in which the atoms of formiate rise to more than one-third of the amount of the acetate.* The same was of course the case with the lead salts. Neither by distillation, nor by crystallisation of lead salts with and without alcohol, nor by crystallisation of baryum salts, have I as yet obtained any pure formiate, although this salt is present in large quantity; but of the prevalent acetates pure crystallisations were obtained. I am therefore unable to determine directly the actual amount of formiates obtained as compared to acetates, but indirectly such determination may of course hereafter be made by destroying the formic acid and distilling the remaining acetic. I estimate that upon five parts of acetic acid the urine yielded one part of formic.

Determination of the Acetic and Formic Acid contained in the Daily Urine of a Man.

The total urine from eleven successive days of a healthy man was concentrated and distilled with H_2SO_4 . A quantity of acid distillate was obtained, neutralised with sodium carbonate and evaporated. The concentrated solution was again decomposed with H_2SO_4 , and the benzoic acid separated. The liquid was again distilled and the distillate boiled with lead carbonate. A quantity of salt was obtained which refused to crystallise, lost acetic acid during evaporation, and became at last partially insoluble in water. From a portion dibasic acetate crystallised. The whole was decomposed and the amount of lead determined as sulphate. This weighed 8.007 gm., corresponding to 5.47 gm. of metallic Pb. This corresponds to 8.59 gm. of lead acetate from urine of eleven days, equal to an excretion of 3.12 gm. in eleven days, or 0.288 gm. per day. I abstain from correcting the data for formic acid on account of what has been stated; its daily amount may be roughly estimated at 0.05 gm.

On the Conditions in which Acetic and Formic Acid may be contained in Urine.

As these acids can only be obtained from urine by processes and agents which effect evident decompositions, such as those of urochrome, it is fair to allow that the volatile acids also may, like benzoic acid, be products of the cleavage of more complicated substances. But it is impossible at present to say what the substances are, and whether the acids are not simply present in combination with some base or other. The latter view might indeed be held if the relative significance could be attributed to the following reaction of urine, which I observed several years ago, and inquired into at some length.

Fresh urine is treated with some milk of lime and filtered; it is then treated with ferric chloride as long as a precipitate is thereby produced, and a slight excess of ferric chloride is added. The filtrate from the ferric precipitate will be found to have a deep red colour, similar to that which ferric salts produce in formiates, acetates, benzoates, succinates, sulphocyanides, and other salts. The reaction has lately been ascribed to sulphocyanide, but for this I have sought without success. I find now that it is yielded also by kryptophanates. Now the urine contains ammonia, which would form with ferric chloride some basic salt, and this also might produce the reaction; the distillate from fresh urine, indeed, shows the reaction beautifully with a drop of ferric chloride. It is therefore quite impossible at present to say whether this reaction is due to any organic acid, much less to which of those which are now all (succinic acid is also alleged by Meissner to be constantly present in urine) shown to be contained in urine.

When urine or its extract is mixed with a moderate quantity of sulphuric acid and boiled a very peculiar state of things ensues, which is not generally understood. The ingredients are not in the presence of sulphuric acid, as it were, at all, but in that of a very slight chemolytic influence only, a kind of contact action. The sulphuric acid is at once enveloped by the attraction of urea, and as long as urea is present no sulphate is formed, except that of ammonia, even on boiling. Although some hippuric acid is decomposed in the extract of urine, and benzoic acid is given out, yet much hippuric acid remains in solution unchanged, and crystallises after the extract has been boiled for hours. If the hippuric acid had been in presence of free sulphuric or hydrochloric acid it must have been decomposed entirely by half an hour's boiling. To the same preserving influence of urea is due the fact that in the distillates obtained during the decomposition of urochrome according to my method, which yields the acetic and formic acid, *no hydrochloric acid is*

ever found. Such acid is only evolved by the addition of a great excess of sulphuric acid to extract of urine, and its effect and advent are unmistakably evident in the fluid. *The mixture becomes black*, and loses entirely its previously red colour. It deposits black charred matter, which differs greatly from uromelanine and the resinous urochrome products. From such charred urine no uromelanine and no pure products of any kind can be obtained. Now these particular conditions, more than anything else, incline me to the opinion that the acetic and formic acid are products of chemolysis of higher organic bodies, and not merely acids set free from salts by sulphuric acids. They escape simultaneously with the carbonic acid gas which is evolved from the urea, and cause a continuous slight effervescence in the fluid. The sulphuric acid does not decompose the kryptophanic acid in the extract any more than the hippuric, *i.e.*, only a portion of it, and that certainly a small one. But when free hydrochloric acid appears the kryptophanic acid disappears, forming, in fact, the great bulk of the black matters in which such decomposing extract of urine abounds. These peculiar reactions must be carefully borne in mind by every one who would successfully study or comprehend these decompositions.

CHAPTER XX.

KRYPTOPHANIC ACID, $C_6H_5NO_5$.

INTRODUCTION.

THIS acid was discovered and first described by me in the Appendix to the "Twelfth Report of the Medical Officer of the Privy Council," 1869, p. 280, and "Journal of the Chemical Society," 23 (1870), 116. It is the principal one of the bodies which constitute the complexity of matters formerly called "extractives;" and which, as I have found, can be almost completely removed from urine by precipitation with ferric chloride. For a short notice of former researches on the free acid and the extractive matters of the urine, see paragraph 19, p. 292 of the Appendix quoted above. All these attempts, without exception, remained without a single tangible result as far as the extractive acids are concerned.

Mode of Isolating Kryptophanic Acid from fresh Human Urine by Lime and Alcohol.

The urine is made alkaline by means of milk of lime, filtered and evaporated. After a while gypsum is deposited and is removed by filtration. The filtrate is subsequently acidified with acetic acid and evaporated to crystallisation, whereby a cake of salt is deposited. After being allowed to stand for some time the mother-liquor (which now forms a syrup) is filtered from this salt cake, and is now ready for treatment with alcohol.

One volume of this syrup is mixed with four volumes of 95 per cent. alcohol, or with five volumes of 90 per cent. alcohol, and shaken in a stoppered bottle, whereupon a voluminous, flaky, adhesive precipitate is formed, and speedily settles down to the bottom of the fluid. The liquor is decanted off, the precipitate shaken with some fresh strong alcohol, and the alcohol again decanted. The bottle and precipitate are now slightly warmed, when the latter gives out much alcohol. The precipitate, which consists mainly of impure kryptophanate of calcium, is next dissolved in a small quantity of water, and the solution filtered through a calico bag, with the aid of pressure. (It is

inconvenient to employ a paper filter, inasmuch as the insoluble impurities have a great tendency to clog the filter.) The solution is again precipitated by means of strong alcohol, and the precipitate is collected in a calico bag and freed from alcohol by pressure. It is now devoid of the soluble urinary ingredients, and by repeating the solution in water and precipitation by alcohol several times, almost pure kryptophanate may be obtained. But it is preferable to adopt one or other of the following processes of purification:—

Purification by Lead Acetate Process.

The crude calcium and sodium salts just described are dissolved in water, and then mixed with a large excess of nearly saturated aqueous solution of lead acetate. The mixture is shaken in a stoppered bottle and then filtered. The filtrate runs through nearly or entirely colourless, while the precipitate which remains on the filter is dark coloured and voluminous. It is washed with the solution of lead acetate, and the washings are added to the rest of the filtrate.

To the filtrate, which consists of lead kryptophanate dissolved in lead acetate, a quantity of alcohol of 95 per cent. is next added. About one volume of filtrate is taken to five or six volumes of alcohol. By this addition of alcohol to the lead solution, there is determined an abundant precipitation of perfectly white lead kryptophanate. This precipitate is separated from the mother-liquor by filtration, and is washed successively with alcohol, water, alcohol, and lastly with ether. Finally it is dried in vacuo, during which process it assumes a slightly yellowish colour on the surface. The precipitate may also simply be washed with water, to remove lead acetate, the basic kryptophanate being also insoluble in water as well as in alcohol. By decomposition with the exact amount of sulphuric acid required, the free acid is obtained, and best transformed into baryum salt by baryta water in excess and a current of carbonic acid. The baryum salt is precipitated by alcohol, redissolved in water, and again treated with lead acetate in excess. The filtrate with alcohol yields pure white kryptophanate.

Purification by Copper Acetate.

To the solution of crude kryptophanates an excess of copper acetate is added, whereupon a voluminous dirty-green precipitate is thrown down, and a greenish-blue solution is produced. The precipitate having been removed by filtration, five or six volumes of 95 per cent. alcohol are added to the filtrate, and cause the production of a voluminous greenish-blue flaky precipitate of kryptophanate. This is filtered, washed with alcohol,

and dried in vacuo over H_2SO_4 . In order to get the copper salt free from lime and soda salts, it is essential to employ such an excess of copper acetate as will leave the mother-liquor blue after all the precipitate has been separated from it. Prior to the drying of the precipitate the copper kryptophanate is soluble in water; subsequently to the drying it is insoluble in water.

From the copper salt the free kryptophanic acid may be obtained by decomposing with sulphuretted hydrogen.

From the lead salt the acid is best prepared by the employment of dilute sulphuric acid.

Mode of Obtaining Kryptophanic Acid from Urinary Extracts after the Removal of all Products of Decomposition by Sulphuric Acid.

Extract of urine is decomposed in the manner described for the isolation of acetic and formic acid (pp. 247 and 248). To the filtrate from the mixed resinous matters, which of course contains a large quantity of ammonium sulphate, an excess of milk of lime is added. It is filtered through a cloth and boiled to drive out all ammonia. It is then acidified with acetic acid, evaporated to crystallisation, and filtered, and to the filtrate alcohol is added, and the subsequent stages of the process are the same as has already been described. The precipitate contains much more potassium chloride than that from fresh urine, and requires special care to be purified from this by one or other of the above processes. It also contains iron, which follows the acid into nearly all its preparations. This is best removed by adding to the solution, freed from calcium by ammonia and ammonium carbonate, a sufficient amount of ammonium sulphide, and filtering immediately. By evaporation the alkali and sulphide are removed, and the solution of the ammonium-salt is ready for the application of lead-acetate.

Mode of Obtaining Kryptophanic Acid from Urine without the intervention of Heat.

The dilute free acid and its acid salts are little affected by heat and air, but the neutral and alkaline solutions (especially when they are impure) become dark under the influence of these agents. It is therefore desirable to be in possession of a method of extraction which shall not involve exposure to the action of heat. In the following process these objections are avoided:—

The filtered fresh urine is treated with lead acetate as long as this reagent gives a precipitate. Experience shows that to every litre of the fresh urine of healthy men, about 40 c.c.

of an aqueous solution of lead acetate saturated at 9.5°C . may be added, and that the precipitate will consist mainly of phosphate and sulphate of lead, there being only traces of organic matter in the precipitate. (From a litre of average urine 6.2 grm. of mixed lead salts were obtained.) To the filtrate a little ammonia is added and a little acetate of lead, so as to obtain a copious precipitate. This precipitate is collected in a calico bag, pressed, washed with water, pressed again, and then decomposed with sulphuric acid in slight excess. It is yellow, and gives a spectrum with a broad absorption band at the beginning of blue. The filtrate is treated with baryum carbonate and a little baryta water. The solution of baryum kryptophanate is now mixed with five volumes of nearly absolute alcohol, whereupon the kryptophanate is precipitated, the urochrome remaining in solution. The baryum kryptophanate is dissolved in water, and again precipitated with lead acetate; the precipitate, after filtration, is digested with a sufficiency of saturated solution of lead acetate and the solution filtered. The filtrate is treated with five volumes of nearly absolute alcohol, whereupon lead kryptophanate falls down in white flakes, which should be washed with alcohol, a little water, alcohol again, lastly with ether, and dried *in vacuo*.

Chemical Properties of Kryptophanic Acid.

It is a transparent, amorphous, gummy solid, very nearly or perhaps entirely colourless. It is soluble in water in all proportions. It is less soluble in alcohol, and still less so in ether. It has a freely acid taste, and decomposes alkaline and earthy carbonates with effervescence, forming solutions of the corresponding salts.

The aqueous solution of the free acid is precipitated by lead acetate, which gives a copious thick white precipitate. It is precipitated by mercury acetate, also by silver nitrate, the precipitate in the latter case being slight.

Mercuric chloride (corrosive sublimate) does not precipitate the free acid. Copper acetate likewise gives no precipitate.

The lead precipitate is redissolved by excess of lead acetate.

Solutions in water of the alkaline and earthy salts of kryptophanic acid are precipitated by excess of strong alcohol. These precipitates darken a little on being heated and fuse, but ultimately become dry and brittle and admit of being powdered, in which state they are endowed with great stability.

Boiled with a great excess of alkaline copper solution they reduce it to suboxide, which at first is in solution, but subsequently if the air be excluded is deposited on further contraction. The alkaline solution fluoresces blue. The aqueous solu-

tions of the alkaline and earthy kryptophanates are precipitated by—

Lead acetate, which throws down a copious white precipitate soluble in excess of the acetate.

Mercury acetate, which gives a white precipitate.

Mercury nitrate, which gives a voluminous white precipitate.

Silver nitrate, which gives a white voluminous precipitate.

The circumstance of kryptophanic acid giving a precipitate with mercury nitrate affects the common urea determination by Liebig's method. Probably an error of from 5 to 10 per cent. on the urea is occasioned by the kryptophanic acid present in the urine.

Iodine dissolved by an iodide, on being added to a solution of kryptophanic acid or of a kryptophanate, produces immediately a precipitate of an iodo-kryptophanic acid wherein one or more atoms of hydrogen have been replaced by iodine. The liquid contains hydriodic acid.

If the solution of the kryptophanic acid be too dilute, there is no precipitate, but only a change of colour indicative of reaction. Thus, on the addition of tincture of iodine to fresh urine there is first of all a precipitate of iodine, just as if the tincture had been poured into water, but very soon the iodine is redissolved, being consumed in attacking the kryptophanic acid. Some few years ago a lively discussion took place in France relative to this subject.

Bromine added to kryptophanic acid or to its salts dissolved in water produces immediately a fawn or light-brown precipitate, being a brominated acid analogous to the iodine compound just referred to.

The kryptophanates on being heated emit acid fumes, but no urinary smell like that given out on heating omicholine is emitted. A residue of charcoal is left which is rather difficult to burn.

Kryptophanic acid prevents the precipitation of ferric oxyde in alkaline solutions. Like oxalic acid it holds in solution prussian blue in presence of free hydrochloric acid.

An ammoniacal solution of silver nitrate becomes immediately very dark on the addition of ammonium kryptophanate. On heating it becomes black (red on dilution), and deposits metallic silver as a black powder.

Nitrate of silver and excess of nitric acid, added to a solution of kryptophanic acid containing urea (to urine with little urochrome and much kryptophanic acid, such as is discharged in certain conditions of the brain, intermittent spasmodic disease) is reduced on standing, and the glass is covered with a silver mirror.

Absorption of Oxygen by crude Kryptophanic Acid in Alkaline Solution.

A quantity of crude kryptophanate of calcium was dissolved in 20 c.c. of water, and enclosed over mercury with 47 c.c. of air, and 14 c.c. of strong solution of caustic potash added. After the lapse of three weeks the 47 c.c. of air had diminished to 38 c.c., so that 9 c.c. of oxygen had been absorbed, equal to 19.1 per cent. of the air employed.

When highly purified, neither kryptophanic acid nor its baryta salt with excess of baryta absorb pure oxygen enclosed with it over mercury.

Kryptophanate of Lead, $C_5H_7PbNO_5$.

The crude kryptophanate of calcium which has been already described, was mixed with excess of a saturated solution of lead acetate, and filtered from the precipitate. The filtrate was mixed with 5 vols. of 95 per cent. alcohol; the precipitate of kryptophanate, a white flaky mass thereby produced, was washed with alcohol, water, and again with alcohol, and lastly with ether. It was then dried in vacuo over H_2SO_4 . During the washing and drying it darkened a little in colour, and ultimately became pale yellow. When quite dry it was found to have shrunk very much.

Analysis (dried in vacuo):—

(1.) 0.3996 gm. with H_2SO_4 and ignited, yielded 0.3104 gm. $PbSO_4$, equal to 53.07 per cent. of Pb. The formulæ $C_5H_7PbNO_5$ + Aq. requires Pb per cent. = 53.62.

The salt further dried at 105° C. lost water, and then furnished the following results:—

Calculated.			Found.			
Atoms.		Per Cents.	1.	2.	3.	4.
5 C	60	16.30	...	15.69
7 H	7	1.90	...	1.89
Pb	207	56.25	55.72	55.73
N	14	3.80	2.89	...
5 O	80	21.75
	368	100.00				

Basic Lead Kryptophanate.

When the neutral salt is washed with water for a long time it loses one-third of its acid, and there remains behind a salt having the composition $2(C_{10}H_{14}Pb_2N_2O_{10})PbO$.

Theory.			Found.		
			1.	2.	3.
20 C	240	14.16	13.05
28 H	28	1.65	1.75
5 Pb	1035	61.06	...	61.2	60.61
4 N	56
20 O	336
	<hr/>				
	1695				

Note.—Analyses 1 and 2 on the same preparation. Analysis 3 on sample prepared in another operation.

Kryptophanate of Copper (with Alcohol).

This salt was prepared by adding a great excess of copper acetate to a solution of the crude kryptophanate of calcium, filtering and precipitating the filtrate with alcohol, washing with alcohol, drying in the steam oven, powdering, and finally drying in vacuo. Prepared in this way, the salt is a compound of alcohol with the copper salt.

	Found.				
	1.	2.	3.	4.	5.
Carbon	28.95	29.53
Hydrogen	4.62	4.67
Copper	24.20	24.67	24.18

The analyses lead to either $2(\text{C}_5\text{H}_7\text{CuNO}_5) + \text{C}_2\text{H}_6\text{O}$ or $2(\text{C}_5\text{H}_7\text{CuNO}_5) + \text{C}_2\text{H}_6\text{O} + \text{H}_2\text{O}$.

Kryptophanate of Copper (without Alcohol).

When the foregoing salt is exposed to moist air, and then dried in vacuo, it loses alcohol, and at the same time changes in colour, becoming very dark green. Analysed in that state, it yielded results corresponding with the formula $\text{C}_5\text{H}_7\text{CuNO}_5$.

Calculated.		Found.			
		1.	2.	3.	4.
5 C	60	27.09
7 H	7
Cu	63.5	27.50	28.82
N	14	...	6.35
5 O	80
	<hr/>				
	224.5				100.00

Dry Distillation of Copper Salt.—8.25 grm. of this salt was subjected to dry distillation, and yielded first water, which was removed from the receiver. Then on heating more strongly a heavy white vapour came over, which was alkaline, smelled of cyanides and of tobacco, and crystallised in white crystals on cooling. It was perhaps cyanide and cyanate of ammonia. It effervesced with platinum tetrachloride, giving a crystalline salt. A dark red oil also distilled over, and this when mixed with HCl and PtCl₄ reduced the platinum to the metallic state and gave a useless black solution. The oil was more soluble in ether than the crystals, so that a separation could be effected thereby.

Kryptophanate of Magnesium.

Free acid prepared by the exact decomposition of the wet kryptophante of lead by means of an equivalent of dilute sulphuric acid, and which contained no sulphuric acid, was mixed with an excess of magnesia, filtered, and the filtrate evaporated on the water-bath. The salt formed a mass like treacle, which, however, after loss of the excess of water, dried up into a brittle mass admitting of powdering. It was powdered and dried at 110° to 120° C.

Calculated.				Found.			
				1.	2.	3.	4.
10 C	. 120	29.56	
14 H	. 14
2 Mg	. 48	11.83		11.45	11.81	11.51	...
2 N	. 28	6.90		6.66
10 O	. 160
2 Aq.	. 36
406							

Dried at from 140° to 160° it lost an atom of water, and became $C_{10}H_4Mg_2N_2O_{10} + Aq.$

Theory.		Found.	
		1.	2.
30.93 C		31.01	...
4.12 H		4.78	...
12.37 Mg		...	12.12

Calcium Kryptophanates.

Some free acid was made by decomposing lead salt with an equivalent of dilute H₂SO₄ (a little baryta water was added, to remove a slight excess of sulphuric acid). An excess of milk of lime, prepared from lime which had been washed, was added to the acid, and the mixture boiled and filtered. To the filtrate about an equal volume of strong alcohol was added, and a precipitate

obtained. This was dried in the water-bath, further dried at 110° , and analysed (Anal. 1, 2, 3). The filtrate was evaporated to dryness, and the lime-salt powdered and dried at 135° (Anal. 4).

Theory.			Found.			
			1.	2.	3.	4.
10 C	120	32.88	33.14	...
13 H	13
$\frac{3}{2}$ Ca	60	16.43	14.85	14.92	...	16.95
2 N	28
9 O	144

365

When kryptophanic acid is boiled with excess of milk of lime, there is produced a salt containing $\frac{2}{3}$ of Ca to 1 of acid. This salt has considerable stability, but appears to be very slowly attacked by the CO_2 of the air. If, however, the salt be dried up and then powdered, one-third of the calcium passes into carbonate, and the dibasic salt $\text{C}_{10}\text{H}_{14}\text{CaN}_2\text{O}_9$ is produced (just as in the case of Ba salt).

Kryptophanate of Baryum.

The magnesium salt was precipitated boiling with slight excess of hydrate of baryum, filtered and evaporated nearly to dryness in the water-bath; refiltered, and the filtrate dried in the water-bath. It formed a perfectly translucent red-brown varnish. Dried at 110° .

Analysis:—

(L.) 445 grm. gave 338 grm. BaSO_4 , equal to 44.66 per cent. Ba. $\text{C}_{10}\text{H}_{14}\text{Ba}_2\text{N}_2\text{O}_{10} + \text{Aq.}$ requires 44.52 per cent. Ba.

This salt took up CO_2 of the air, and formed a deposit of BaCO_3 . The solution on evaporation to dryness left a residue, which, dried at 110° , contained 36.28 per cent. Ba.

It would also seem that there is a baryta salt of the formula $\text{C}_{10}\text{H}_{11}\text{Ba}\frac{2}{3}\text{N}_2\text{O}_{10}$.

Metamorphosis of Baryum Kryptophanate into an Acid Salt by Boiling with Water.

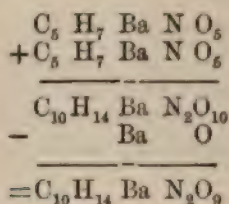
15.5 grm. of copper kryptophanate (containing a certain quantity of alcohol) was decomposed with hydrothion and filtered. The filtrate was boiled for a long time with BaCO_3 and some BaH_2O_9 , and gave off some ammonia. It was subsequently filtered. The precipitate on the filter contained much carbonate, and probably and apparently no organic product of decomposition. The filtrate was mixed with a large quantity of 98 per cent. alcohol, whereupon a pale yellowish-white baryum salt was precipitated. This salt was washed with alcohol of 98 per cent.

(the wash alcohol was strongly alkaline) dissolved in water, and the aqueous solution boiled. Thereupon ammonia was again evolved and abundance of baryum carbonate precipitated. This was removed by filtration, the filtrate evaporated to dryness at 110° and powdered. It formed a gummy mass, offering no difficulty to comminution. The total amount of baryum salt obtained was 4.377 grm.

The analyses lead to the formula $C_{10}H_{14}BaN_2O_9$.

Calculated.			Found.		
			1.	2.	3.
10 C	. 120	27.09	26.84
14 H	. 14	3.16	3.87
Ba	. 137	30.93	31.75
2 N	. 28	6.32	...	5.94	...
9 O	. 144	32.50
	443	100			

The reaction by which this salt is produced is the loss of baryum oxyde, thus:—



This salt gave a white precipitate with $AgNO_3$, soluble in HNO_3 . It gave a white precipitate with lead acetate, soluble in acetic acid. It gave no reaction with copper acetate, zinc chloride, or calcium chloride. With mercuric chloride it gave a white precipitate, soluble in HNO_3 ; with mercuric nitrate the same; with mercurous nitrate a precipitate which, apparently white at first, became quickly dark. The solid baryum salt, moistened with strong H_2SO_4 , appeared to give a double sulphate of baryum and kryptophanate.

Kryptophanates of Cobalt.

A solution of kryptophanic acid (some of the same sample as that employed for magnesium salts) was treated with cobalt carbonate; effervescence ensued both in the cold, and more on boiling. A red solution was obtained and precipitated by 2 volumes of alcohol of 94 per cent. A pale pink precipitate ensued which was filtered off. On drying in the steam-bath it shrunk, then fused like the calcium and other salts, and soaked

the paper like fat (of this the greater portion dissolved in warm water, with red colour as before). It ultimately became hard, was white rose coloured in the interior of the lumps. Powdered and dried at 100° to 110° .

Determination of Cobalt.—0834 grm. burned and reduced in H atmosphere gave 014 grm. or 16.78 per cent. Co. The formula $C_{10}H_{16}CoN_2O_{10}$ (At. W. = 328.8) requires 15.36 per cent. Co.

The formula $C_{10}H_{14}CoN_2O_9$ requires 16.19 per cent. Co.

Solution in Alcohol.—Was of a rose red colour, and on evaporation in platinum dish became indigo blue wherever it dried, and was ultimately a deep blue hard mass. It was dissolved in water and became red again, filtered from slight precipitate and again evaporated. Dried at 110° . On heating, it swelled up greatly, gave out a stinking gas, and left a residue of cobalt and carbon. This had to be treated with nitric acid to deflagrate all carbon, after which the cobalt was reduced in H atmosphere.

Determination of Cobalt.—2897 grm. left after the before-mentioned treatment 08 grm. Co or 27.7 per cent. Co. The formula $C_{10}H_{14}Co_2N_2O_{10}$ (At. W. 489.6) requires 26.7 per cent.

$C_{10}H_{12}Co_2N_2O_9$ requires 27.9 per cent.

Silver Salts.

When a solution of a tetrabasic kryptophanate, as, for instance, the magnesium salt, $C_{10}H_{14}Mg_2N_2O_{10}$, is mixed with a solution of silver nitrate, there is produced a dark grey precipitate, which either has not a definite composition or else suffers decomposition spontaneously or on washing. The following determinations of silver in different specimens of the precipitate will serve to illustrate the inconstancy of its composition after having been washed and dried:—

	Percentage of silver.
Precipitate <i>a</i>	77.2
Do. <i>b</i>	60.08
Do. <i>c</i>	56.56

Precipitate *a* was prepared by using a *very small proportion* of silver nitrate to precipitate the magnesium kryptophanate. It was washed, dried in the steam-bath, and finally dried at 100° to 110° .

Precipitate *b* was washed six times with a small quantity of water and dried in vacuo.

Precipitate *c* was very little washed, and then pressed and dried in vacuo for several days.

Thus it appears that by dint of washing decomposition of the silver salt is effected, so as to give a salt richer in silver than the original precipitate.

Precipitate *c*, which may be regarded as the least altered specimen of the precipitated silver salt, roughly approximates in composition to the formula $C_{10}H_{14}Ag_4N_2O_{10} + 2 Aq.$, corresponding with the magnesium salt from which it was formed. The following are the details of its preparation and analysis:—

3 gramm. of silver nitrate were dissolved in water and precipitated with 8 c.c. of very concentrated solution of tetrabasic magnesium kryptophanate. The dark-coloured precipitate, after slight washing, pressing, and drying *in vacuo* for several days, weighed 1.603 gramm.

The formula $C_{10}H_{14}Ag_4N_2O_{10} + 2 Aq.$ requires

Calculated.			Found.
10 C	120	15.2	13.08
18 H	18
4 Ag	432	54.7	56.56
2 N	28
12 O	192
790			

(It will be understood that the insufficiency of the washing would occasion the carbon to be too low, and the ignited residue to be too high for the real quantity of silver.)

The interpretation which is to be put on the data given by this examination of the silver salt appears to be the following:—The tetrabasic silver salt is very perishable, and breaks up into tribasic silver salt and silver oxide. By washing, tribasic silver salt is more or less perfectly dissolved out, and silver oxide accordingly accumulates in the precipitate.

The stable silver salt of kryptophanic acid appears to be the tribasic salt, and is formed by double decomposition, when either a dibasic or a tribasic kryptophanate is added to a solution of silver nitrate. It is white, and appears to be rather soluble in water.

a. Some silver salt obtained by double decomposition between dibasic calcium salt and silver nitrate was washed and dried *in vacuo*. 1.110 gramm. gave .0570 gramm. of metallic silver, or 51.35 per cent. Ag.

b. Some silver salt prepared from dibasic baryum salt and silver nitrate, and dried *in vacuo*, gave 52.80 per cent. Ag.

c. Another quantity of silver salt made from a specimen of calcium kryptophanate, believed to be the tribasic salt, had the following history:—

Calcium kryptophanate, obtained from fresh urine by lime and alcohol process, purified twice by resolution in water and precipitation by alcohol, was boiled with animal charcoal to decolorise it, and then mixed with silver nitrate as long as a preci-

pitate was produced. The precipitate, white at first, became slightly coloured grey. It was washed, ultimately boiled with alcohol, dried at 100° to 110°. At 130° it became brownish on surface.

Calculated.			Found.						
			a.	b.	1.	2.	3.	4.	5.
10 C	120	19.08	19.97	...
13 H	13	2.07	2.49	...
3 Ag	324	1.53	51.35	52.80	53.1	53.8	52.8
2 N	28	4.45	5.7
9 O	144
629									

Theoretical Considerations respecting Kryptophanic Acid.

Kryptophanic acid is supposed in some of the foregoing paragraphs to be a dibasic acid of the formula $C_{10}H_9NO_8$. But it is evident that it may be considered as tetrabasic, and to have the formula $C_{10}H_{18}N_2O_{10}$. In that case the metallic salts will have the general formula:—

Examples: Lead salt	$C_{10}H_{14}Ml^I_4N_2O_{10}$
Do. hydrated	$C_{10}H_{14}Pb_2N_2O_{10}$
Basic	$C_{10}H_{14}Pb_2N_2O_{10} + 2 Aq.$
Copper salt	$2(C_{10}H_{14}Pb_2N_2O_{10}) PbO.$
Do. with alcohol	$C_{10}H_{14}Cu_2N_2O_{10}$
Magnesium salt	$C_{10}H_{14}Cu_2N_2O_{10} + C_2H_6O.$
Do. dihydrate	$C_{10}H_{14}Mg_2N_2O_{10} + Aq.$
Baryum salt	$C_{10}H_{14}Mg_2N_2O_{10} + 2 Aq.$
Do. tribasic	$C_{10}H_{14}Ba_2N_2O_{10} + Aq.$
Do. acid	$C_{10}H_{13}ba^I_3N_2O_{10}$
Calcium salt	$C_{10}H_{14}Ba N_2O_9$
Do. acid	$C_{10}H_{13}ca^I_3N_2O_9$
Cobalt salt acid	$C_{10}H_{14}Ca N_2O_9$
Do. basic	$C_{10}H_{14}Co N_2O_9$
Silver salt	$C_{10}H_{13}Co_2N_2O_9$
	$C_{10}H_{13}Ag_3N_2O_9$

CHAPTER XXI.

CARBONIC ACID, CO_2 .

HISTORY AND LITERATURE.

PROUST ("Ann. Chim." 36 (1800), 260) observed that the froth which gathers on urine when it is evaporated contains a mixture of carbonic acid gas and air. Most chemists, however, doubted that this acid was contained in the urine as such, but believed it to be a product of the decomposition of urea by heat. A. Vogel ("Schweigger's Journ." 11 (1814), 401), therefore, to test the assertion of Proust, placed one litre of urine in a bottle of two litres capacity, and closed the bottle with a cork, from which a bent tube led to a small cylinder filled with lime water. This apparatus was placed under the bell-jar of an air-pump, and the air gradually exhausted. As the air from the flask passed through the lime water it caused a white precipitate in this agent; the evolution of gas continued for about two hours. The urine in the bottle forms a great froth, and care must be taken not to let any particle of froth rise into the lime water. On destroying the vacuum, lime water will of course rise into the urine. The quantity of lime water and carbonate formed thus lost may be limited by letting the bent tube dip only very little into the lime water.

Occurrence and Chemical Characters.

Carbonic acid is the principal product of the perfect combustion of carbon and carbonaceous substances. It is therefore the main product of the process of oxydation carried on in all animal bodies, and is exhaled from them by means of the lungs. In urine, as in other animal fluids, the blood excepted, there is only such a quantity of carbonic acid present as corresponds to the power of absorption of its water. Carbonic anhydride is a coercible gas of considerable chemical affinity for bases. It gives a white precipitate in lime water, which is again dissolved by an excess of the carbonic acid. Acetate of lead produces in very dilute solution of the gas in water a white turbidity. The gas is completely absorbed by caustic potash in solution, or even by caustic potash in solid pieces, when there is sufficient opportunity for contact.

*Mode of Determining the Quantity of Carbonic Anhydride
contained in Urine by Volume.*

Whenever small quantities of carbonic anhydride have to be estimated, it is best to treat them volumetrically. In the case of the carbonic anhydride in urine, the following proceeding will be found most efficacious and secure:—A two-necked Wolff's bottle is connected with a graduated pipette containing the urine, and provided at its lower end with a glass stopper. The second neck of the Wolff's bottle is connected with a second two-necked Wolff's bottle containing some cotton-wool. This is connected with a Sprengel's mercurial pump, the delivery tube of which can be made to communicate with a gas-measuring tube filled with mercury. When the apparatus has been exhausted by the action of the pump, a measured quantity of the urine to be tested is allowed to flow from the pipette into the first Wolff's bottle. This urine will immediately begin to froth, and on the application to the bottle of some warm water to boil. The froth will pass into the second bottle, and be retained and destroyed there. The carbonic acid will pass into the gas-measuring tube, with which the delivery tube of the pump has been connected after the vacuum was obtained and before the urine was allowed to flow into the first bottle. The gas ultimately collected over the mercury is measured with the usual observations of air-pressure and temperature. It is next treated with some caustic potash, and the amount of gas absorbed is again ascertained with the precautions mentioned. From the volume absorbed the weight of the carbonic acid and its proportion to the weight or volume of the urine employed are calculated.

*Mode of Estimating the Quantity of Carbonic Acid contained in
Urine by Weight.*

From a measured quantity of urine the carbonic acid is evolved by warmth and diminished air pressure, and caught in baryta water. This is the principle of the analysis; the following are the particulars:—100 c.c. of urine are put into a strong flask, closed by a cork, which is pierced by two glass tubes. One tube dips into the urine, and above the cork is drawn out into a long point, and closed by the blowpipe. The second tube begins with the cork, has a double bend, and is connected with a second, but empty bottle, out of which a second doubly bent tube leads to a third flask half full of clear baryta water. Several bottles with baryta water may yet be attached. To the last one the air-pump is fixed. The whole apparatus being made air-tight, the flask containing the urine is placed in the water-bath, and its temperature raised to 60°, after which the air is gently pumped out of the apparatus. The urine soon begins to

boil, and distils partly into the empty bottle, and the solution of baryta in the several bottles becomes turbid from carbonate of baryum. After the lapse of about half an hour or more, the thin point of the first tube is broken off, and air is gently drawn through the apparatus. The carbonate of baryum is afterwards separated by filtration, washed, and dissolved in hydrochloric acid; the solution is precipitated by sulphuric acid; and from the weight of sulphate of baryum thus obtained the amount of carbonic acid is calculated.

Physiological and Pathological Indications.

From the observations of Planer ("Zeitschr. d. Gesellsch. d. Aerzte Wiens," 1859, p. 465) and Ewald ("Archiv. f. Anat. u. Physiol. von du Bois-Reymond und Reichert," 1873, p. 1), it appears that the urine excreted by persons under the influence of the febrile process contains more carbonic acid than the urine of the same persons at a period during which they are free from fever. Cases of recurrent enteric fever and pneumonia were examined. The carbonic acid rises and falls in a manner parallel with the rising and falling of the excretion of urea. A part of the carbonic acid contained in the urine is probably derived from the blood, another directly from the tissues surrounding the walls of the bladder (Strassburg, Pflüger's "Archiv." 3).

CHAPTER XXII.

CHLORINE AND CHLORIDES OF SODIUM AND POTASSIUM.

INTRODUCTION.

A PHYSIOLOGICAL law makes these substances the common accompaniments or ingredients of our food. Salt is a necessary to man and animal, and nature finds means and ways to supply it to both. Like oxygen, these salts are found everywhere. Their solubility in water equals the diffusibility of oxygen; they are carried from the sea by wind, rain, and clouds over large tracts of country, and thus they penetrate the masses. There is probably no kind of water on the globe which does not contain them, and consequently they pervade vegetable and animal structures. Of all waters, sea and mineral water contain the greatest abundance of them. They occur, moreover, in a solid crystalline state, mostly imbedded in layers of gypsum. Of the mineral rock salt we have to make an important use in the quantitative analysis of the chlorides of the urine; for no salt being so pure as rock salt, a solution of it in water serves as the basis for the preparation of all the tests which are required for the volumetrical method.

CHLORIDE OF SODIUM, NaCl

Physical and Chemical Properties.

Chloride of sodium crystallises in the cubic system. The cleavage of rock salt leads to a cube, and crystallisations of salt from pure solutions always assume this form. If, however, certain organic substances are mixed with the solution, the crystallisation will ensue in the form of the regular octahedron. Chloride of sodium, therefore, when crystallising out of the urine or other animal fluids, always appears in octahedra. The latter are best obtained by evaporating a large amount of (one day's) urine to a thin syrupy consistence, and letting it stand over night. The crystals will be found in the sediment on decanting the supernatant fluid.

Chloride of sodium dissolves in water of from 12° to 24°

invariably at the rate of 31·84 parts in 100 parts of the saturated solution. For procuring the latter clear rock salt is best used as already described under Urea.

In solutions of chloride of sodium, nitrate of silver produces a white precipitate, which is insoluble in nitric and hydrochloric acids. We make use of this test for removing chlorides from the urine when we wish to ascertain accurately the amount of urea by the volumetrical method. In the same solutions the nitrate of the suboxyde of mercury produces a precipitate of calomel (subchloride of mercury).

If a concentrated solution of chloride of sodium is mixed with a similar solution of nitrate of oxyde of mercury, nitrate of sodium and bichloride of mercury (corrosive sublimate) are formed, the latter transforming the fluid into a white magma of crystals. The same juxtaposition takes place in dilute solutions, with the difference, however, that the fluid remains clear, because the sublimate is kept in solution. In solutions which contain chloride of sodium and urea at the same time, no precipitation of urea by nitrate of oxyde of mercury will take place as long as any chloride of sodium is yet present untransformed into nitre and corrosive sublimate. Upon this test is based a volumetrical determination of the quantity of chlorine.

Diagnosis of Chlorine in Urine.

Some urine is mixed with strong nitric acid, and an excess of nitrate of silver added. A voluminous precipitate ensues, which by agitation and warming collects in a curd-like clot. The supernatant fluid is now decanted, and the precipitate boiled with a fresh quantity of nitric acid to dissolve some impurity; it is again washed with water by decantation, and dissolved in strong caustic ammonia. Excess of nitric acid added to this solution reproduces the white precipitate, which is chloride of silver. By fusing this precipitate in a porcelain crucible and weighing it, an accurate determination of chlorine is obtained. Chlorine may be obtained from urine or from chlorides obtained from it by crystallisation by heating them with some peroxyde of manganese and sulphuric acid. By heating a concentrated specimen of urine with a large excess of sulphuric acid chlorine is obtained as hydrochloric acid in a distillate, which also contains formic and acetic acid and a volatile oil. The hydrochloric acid passes last. The more detailed description of this process will be found under the chapter relating to urochrome and to acetic and formic acid.

Mode of Obtaining Chloride of Sodium from Urine.

The urine is evaporated to one-eighth and filtered. The filtrate is evaporated on the water-bath to a thin syrup and

allowed to cool gradually. After twenty-four hours crystals will be found deposited, which, if they are few in a fluid extract, may be chloride of sodium only in octahedra; but if the crystallisation takes place from a more concentrated extract, the crystals deposited in hard crusts are a mixture of chloride of sodium with a compound of chloride of sodium and urea. With these phosphate of sodium and phosphate of sodium and ammonium are always mixed when the extract was very concentrated or was cooled down very slowly.

From the crystals so obtained after draining, pressing between bibulous paper in a press or vice, redissolving in water and boiling with animal charcoal, chloride of sodium may be obtained by fractional crystallisation. It is, however, easier to calcine the salt as it comes from the press, to destroy urea and colouring matter, and to crystallise the filtered solution of the residue, when pure chloride of sodium crystallises first, and phosphate of sodium and any potassium salts remain in the mother-liquor.

Chloride of Potassium, KCl.

The potassic chloride in urine being present in smaller quantity than the sodic salt, and crystallising in the same cubic form cannot easily be obtained by direct crystallisation. It may, however, be precipitated from the concentrated urine by adding to this a quantity of alcohol, and after removal of any precipitate by filtration, a sufficiency of platinic chloride. The crystals of potassic chloride platinic chloride, which form on standing, may be recrystallised from hot water, decomposed by a dull red heat, and then the potassic chloride may be extracted from the platinum by water and crystallised.

Method of Determining the Quantity of Chlorine in Urine by means of Nitrate of Oxyde of Mercury.

From the analysis of urea we are already acquainted with the fact that nitrate of oxyde of mercury produces a copious white precipitate in a solution of urea. This precipitate is not produced with corrosive sublimate.

On mixing a chloride of any of the alkali metals with nitrate of oxyde of mercury, a transmutation of the two salts into corrosive sublimate and a nitrate of the alkaline base takes place. We have already seen the result of this process as regards chloride of sodium.

If a solution of urea is mixed with some chloride of sodium, and a dilute solution of nitrate of oxyde of mercury is then added in small portions, a white turbidity occurs on the spot where the two fluids mix with each other; but this turbidity immediately disappears if the fluid is shaken a little, and the latter remains as clear and transparent as before the addition of

to nitric, which is soluble in sodium. It would have remained permanently there. In the addition of the nitric acid required, the mercury will disappear with the whole of the chloride in the solution, and the nitric acid will be consumed. From the loss of acid from the mercurial solution produced, a sufficient quantity of it is found.

From the loss of acid, the loss of the amount of mercury contained in the solution of the nitrate of the oxide of mercury, which has been added to the solution of urea containing a known amount of chloride of sodium, until the permanent turbidity was produced, the amount of chloride, or chloride of sodium, contained in that solution may be also known. The loss of mercury of the mercurial solution consumed, exactly corresponds to one atom of chlorine or chloride of sodium.

In the contrary, if the amount of chloride of sodium contained in the solution of urea is known, and the amount of mercury contained in the mercurial solution is unknown, it is easy to calculate the amount of mercury contained in the mercurial solution used.

The proceeding for ascertaining the amount of chloride of sodium is particularly applicable to the urine, because the addition of urea is here not required. It may, of course, be used with advantage for ascertaining the amount of chlorine contained in brine or sea-water, and generally speaking, in all cases where a large number of analyses have to be made in the shortest possible time. If, however, the amount of chlorine to find is not being urine is to be determined, the proceeding has to undergo some modification.

I have already described the simplest mode of obtaining solutions of the nitrate of the oxide of mercury. Care must be taken not to use the common mercury of commerce, because it always contains lead and bismuth, which render the analysis of chloride of sodium uncertain. If either lead or bismuth be present in a solution of mercury, it will, on the latter being mixed with a solution of urea containing chloride of sodium, immediately cause a white turbidity or opalescence, which makes it impossible to see distinctly the point at which the combination of urea and oxide of mercury begins to be precipitated.

If, therefore, it is the intention of the operator to use the common mercury of commerce, it will be best for him to transform it into crystallized persulfate or nitrate of suboxide of mercury, by boiling an excess of the metal in dilute nitric acid, concentrating and cooling the solution. The crystals of this salt are then separated from the mother-liquor, which contains the foreign metals; they are washed with dilute nitric acid, twice with a little water, by which process a part is trans-

formed into basic salt. If the commercial nitrate of the suboxyde be used, this process of washing must always be gone through, because the manufacturers simply remove the crystals from the mother-liquor without washing them. Small pieces of the crystallised salt should not be used at all, because the yellowish mother-liquor adheres to them with such pertinacity, that it is difficult to remove it by washing without dissolving the greater part of the salt also.

The crystals of nitrate of suboxyde of mercury are now dissolved in nitric acid, and heated until the evolution of vapours of nitrous acid has entirely ceased, and a drop of the solution is no longer precipitated by chloride of sodium. The solution, after evaporation on the water-bath to a syrupy consistence, is diluted with ten times its own volume of water. If, after the lapse of twenty-four hours, any basic salt of the protoxyde has been precipitated, it may be removed by filtration.

In order to make this solution serviceable for the quantitative analysis of chloride of sodium it must be graduated, so as to contain a definite amount of nitrate of oxyde of mercury in a given volume. This may be effected in two ways. It is either graduated directly by means of a solution of chloride of sodium of known strength, or, after the amount of oxyde it contains has been determined, it may be diluted with as much water as is necessary, in order to make one cubic centimetre of this dilute mercurial solution indicate exactly 10 milligrammes of chloride of sodium. For both proceedings a solution of chloride of sodium is required, containing a known amount of this salt. The preparation of the standard saturated solution has already been described. Of this saturated solution we take with a pipette, observing the usual caution, 20 c.c., and add 298.4 c.c. of water, whereby we obtain 318.4 c.c. of dilute solution of chloride of sodium, containing in all 2×318.4 milligrammes of chloride of sodium; 10 c.c. of this solution contain, therefore, 200 milligrammes of chloride of sodium.

Preparation of Mercurial Solution Graduated for Chloride of Sodium.—Ten cubic centimetres are measured by means of a small pipette delivering exactly that amount of fluid after having been filled up to the mark on the narrow tube. These 10 c.c. are poured into a small beaker; to this are added 3 c.c. of a solution of urea, containing in 100 c.c. 4 grammes of urea, in 1 c.c. therefore 40 milligrammes of urea. For measuring this latter solution a narrow test-tube is very serviceable, when marked with a file at the point to which it will be filled by any 3 c.c. of fluid.

The dilute solution of mercury to be graduated is now filled into a dropping glass or burette, and from this, and after noting down the level, it is added in drops to the solution of chloride

of sodium containing urea, which is kept in a rotatory motion. The formation of a distinct and permanent precipitate indicates the completion of the test. An opalescence of the fluid must not be mistaken for the precipitate of urea and protoxyde of mercury. It is caused by a trace of foreign metal; it may easily be recognised as not proceeding from the completion of the test by the circumstance, that after its appearance the turbidity is not increased by the addition of a few more drops of the mercurial solution. If the precipitate has been caused by the compound of urea, every additional drop of the mercurial fluid produces an increase of the precipitate, and therefore makes the fluid thicker than it was before.

In graduating these fluids, I generally take the following precaution:—I measure 10 c.c. of water into a beaker, add 3 c.c. of the solution of urea, and then one or two drops of the mercurial solution to be graduated. The amount of precipitate thus produced shows the limit to which the addition of mercurial solution to the fluid containing a known amount of chloride of sodium must be carried, in order to be safe against the error from the opalescence of the mixture.

Suppose that there have been used for the production of the precipitate, in 10 c.c. of the solution of chloride of sodium, 7.8 c.c. of the mercurial fluid, the latter is too concentrated to admit of accurate graduation; it is therefore diluted with its equal volume of water, and then tested a second time. Suppose that there have now been used, for 10 c.c. of the solution of chloride of sodium mixed with urea, 15.5 c.c. of the mercurial solution for the production of a permanent precipitate, then we add, to every 155 volumes of this mercurial solution, 45 volumes of water, whereby we obtain 200 volumes of a mercurial solution, of which 200 c.c. exactly indicate 200 milligrammes of chloride of sodium, or one cubic centimetre 10 milligrammes of chloride of sodium.

If, in the first test, we use 2.7 c.c. for 10 c.c. of solution of chloride of sodium, we then add five or six times the amount of water to it. The mercurial solution, which is to be graduated, must not be too different in concentration from the fluid required for the test, and which we are desirous of producing.

We finally ascertain the correctness of the measurements by an experiment. The degree of permanent precipitate produced by the addition of 20 c.c. to 10 c.c. of the solution of chloride of sodium and urea, must be borne in mind when performing the actual analysis for practical purposes. The only source of error connected with this quantitative analysis of chloride of sodium, is that an excess of the mercurial solution may be added, so that the precipitate is formed in excess; or that too little of the solution may be added, so that the turbidity is insufficient. But a

little practice, and the caution recommended above will soon teach us how to avoid this error.

The test-fluid, the preparation of which has just been described, is calculated for those cases in which, besides chlorides, there are no other salts, and no excess of urea in solution. It is liable to lead to a small error, when used for the determination of chloride of sodium in the urine, which makes its apparent amount in urine smaller than in reality it is. This error is occasioned by the earlier appearance of the critical precipitate at the completion of the test, in cases where much urea and other salts are present, because the precipitate is less soluble in the more concentrated fluids. A deposit of nitrate of urea and protoxyde of mercury is of course not formed in the fluid, before the latter is saturated with the former. The mercurial solution always contains free nitric acid, which dissolves more of the nitrate of urea and protoxyde of mercury than water, and the latter more than a solution of nitrate of urea.

But as urine generally contains more urea than has been added to the solution of chloride of sodium for the purpose of its graduation, this urea takes a part of the free nitric acid of the mercurial solution, forming nitrate of urea, which diminishes the solubility of the precipitate in the fluid. As the precipitate in that case appears earlier, less test-fluid is used for producing the critical test. This error may be completely avoided by adding to the 10 c.c. of solution of chloride of sodium, to which 3 c.c. of the solution of urea have been added, 5 c.c. of a solution of sulphate of sodium, saturated at the ordinary temperature of the air, and then graduating the fluid.

Nitrate of oxyde of mercury, when added to a solution of sulphate of sodium, produces a yellow pulverulent precipitate of turpeth mineral. If the sulphate of sodium contain chloride of sodium, the addition of the nitrate of oxyde of mercury will not form a precipitate of turpethum before the whole of the chloride of sodium has been transformed into sublimate, and the addition of the sulphate of sodium modifies the experiment only in one way, namely, by the combination of the free acid of the mercurial solution with the sulphate of sodium an acid salt is formed, which has the same effect as an excess of urea.

On adding urea, and afterwards nitrate of oxyde of mercury, to a solution of sulphate of sodium which does not contain any chloride of sodium, and may be tolerable dilute, the mixture becomes a gelatinous magma of a snowy-white combination, which contains sulphuric acid, urea, and oxyde of mercury, and is a little less soluble in water than the corresponding nitrate.

The Fluid applied to the Urine—Special Proceedings.—Before the fluid can be applied to the urine, it is necessary to remove the phosphoric acid from the latter. This is done by the solution of baryta in the manner described in the analysis for urea. The fluid filtered from the precipitate is alkaline from an excess of baryta. This alkaline reaction must be removed by the addition of nitric acid. The correctness of the analyses to be made mainly depends upon the caution not to add more nitric acid to the filtered liquid from the baryta precipitate than is just necessary to produce a faint acid reaction. For this reason it is advisable to acidulate the whole filtered liquid before taking any part from it by means of dilute nitric acid; an excess of one drop of acid in 100 c.c. of fluid is of no consequence, while it would interfere with the accuracy of the analysis when added to the smaller quantity used for analysis.

For the test we take 15 c.c. of the acidulated fluid, corresponding to 10 c.c. of urine. This is done by means of a small pipette which exactly delivers 15 c.c. when filled to the mark in the narrow tube. The measured quantity is delivered into a small beaker, and being kept in a rotary motion the mercurial solution is made to flow into it. After the turbidity has appeared, the amount of test-fluid used is read off the scale of the burette; every cubic centimetre used corresponds to 10 milligrammes of chloride of sodium.

The presence of chloride of sodium in the urine requires some modifications of the analysis for urea, which has already been described in the paragraph relating thereto. There it has been stated that, for very accurate analysis, the removal of the chlorine from the urine before the addition of the fluid graduated for urea became essential, and a graduated solution of nitrate of silver to be used for that purpose was described. In this case the analysis of chloride of sodium, by means of the mercurial solution, serves to indicate exactly the amount of solution of silver (graduated for the same amount of chloride of sodium as the mercurial solution) which has to be added to the urine for precipitating the whole of the chlorine contained in it.

Daily Average Amount of Chlorine Discharged during Health.

The chlorine in urine is in combination with sodium and potassium. The reader is specially cautioned not to confound figures expressing the amount of chlorine with those expressing the amount of chloride of sodium, or potassium.

Observations of the daily average amount of chlorine discharged by persons of different sexes and ages were made by Bischoff. His results are as follows :—

	Chlorine in Grammes.
Adult man, living well, discharged	8.7
Woman, 43 years of age, "	5.5
Girl, 18 years, " "	4.5
Boy of 16 years, " "	5.3
Boy of 3 years, " "	0.8

Hegar published a series of observations made upon eight students at the University of Giessen. The daily average of chlorine discharged he found to vary in different individuals, and to fluctuate between 7.4 and 13.9 grm. This gives for one individual of that class a daily average of 10 grm. of chlorine, and calculated for one hour it gives 0.44 grm. of chlorine. For the average of adult persons, however, the medium amount of chlorine discharged during twenty-four hours is not quite so high, and for the majority of adult individuals we may assume 6 to 8 grm. as the average of chlorine discharged during twenty-four hours, which, calculated for one hour, gives 0.25 to 0.33 grm. of chlorine. The figures given by Bischoff show some relative quantities in women and children.

That the amount of chlorine discharged during twenty-four hours varies in different individuals, undoubtedly depends mainly upon the fact that unequal amounts of chloride of sodium and potassium are ingested with the food by different persons. Sailors, who have lived on salt rations for the greater part of their life spent afloat, will discharge an extraordinary amount of chlorine in their urine, because the ordinary food of our kitchens is insipid to them without the addition of an amount of salt that would make any ordinary person ill. Such men may be seen dipping sweet cake into salt, and this inclination generally lasts for the remainder of their life on land. Common life shows how different are the tastes of individuals relative to the amount of salt in their food, and leads us to expect the differences which indeed we find.

The amount of chlorine discharged by an individual varies on different days, according to and corresponding with the amount of chloride of sodium and potassium taken with his food. When Falck ate strongly salt food on three successive days, he discharged the following respective amounts of chlorine, namely, 6.0, 7.8, and 10.3 grm. during twenty-four hours. But when he partook of food containing no addition of salt, he discharged 2.5, 1.6, and 0.9 grm. of chlorine on the three respective days succeeding the experiment. Vogel observed the amount of chlorine discharged per hour by several individuals who had taken common salt in doses not sufficiently large to purge them. In all, the amount of chlorine discharged per hour was increased, and rose from 0.4 grm. to 1.0, nay, even 1.8 grm. In some, the

chlorine which had passed into the blood was discharged again by the urine rapidly and in large quantities; while in others the discharge lasted longer, and the quantities for equal times were smaller.

The largest amount of chlorine per hour is secreted a few hours after the largest meal of the day, the smallest amount is invariably secreted during the night (sleep). In eight individuals examined by Hegar the average amount of chlorine discharged per hour was, in the afternoon, 0.57; in the night, 0.28; in the forenoon, 0.48 gm. In one and the same person the average amount of chlorine per hour would vary between 0.20 as minimum and 1.32 gm. as maximum per hour, so that the maximum was more than six times as large as the minimum. From this we must conclude that *the secretory activity of the kidneys, as regards chlorine, is diminished during rest and sleep.* Though the blood be rich in chlorine taken with the food in the evening, yet the lowest amount of chlorine is discharged during the night. *Mental and bodily activity, on the other hand, will increase the secretory activity for chlorine of the kidneys at any time during the day or night.* This is particularly striking in the morning. For, though a person after a supper containing plenty of salt may secrete a very small amount of chlorine during the sleep of the night following, and for breakfast may take food containing no addition of salt, or no food at all, or only a tumbler-full of water, yet the amount of chlorine discharged during the hours of the forenoon, when the mind and body are most active, and when the nutritive changes of the body are being rapidly effected, will be double the amount of that during the night. It will of course rise still more, if food containing an addition of salt be taken. The amount of chlorine discharged after a substantial English breakfast, with meat and eggs, is therefore considerably larger than that discharged after the Continental *café au lait*, or the coffee and hot rolls of the German student. Hegar found that a person who used to be given to mental labour discharged more chlorine per hour of the night (0.47 gm.) than during the same time in the morning, when the quantity was only 0.44 gm. Vogel observed frequently an instantaneous increase in the amount of chlorine secreted by the urine under the influence of increased mental and bodily labour. We have already seen that the same causes exert a similar influence upon the total quantity of urine discharged, and upon the amount of urea secreted with it. There can be no doubt that most of the ingredients of the urine share this fate, as we have seen or shall see more particularly under the history of the single substances. Vogel states, moreover, that by the ingestion into the system of large quantities of water, which stimulate the kidneys, not only the amount of urine and urea, but also of chlorine is increased. After the stimulus has ceased, there fol-

lows a period of relaxation; during which the activity of the kidneys becomes lessened, and less chlorine than usual is excreted. A person whose hourly secretion of chlorine during the night was 0.13 grm., drank four pints of water in the evening. The hourly amount of chlorine rose to 0.60 for several hours, fell then to 0.12 grm., and somewhat later to 0.10 grm. In the morning, however, though no breakfast had been taken, the amount of chlorine was raised to 0.51 grm. by horse exercise. Another person drank four pints of water in the afternoon after dinner, whereby the hourly amount of chlorine towards and during the evening rose to 1.89 grm.; during the night it amounted to 0.57 grm., being 0.19 in excess of the usual average. On the next morning the same individual drank again two pints of water; but, notwithstanding this, the hourly amount of chlorine remained below the normal average during the entire day, amounting only to 0.42 grm., sinking in the night following as low as to 0.014, rising a little on the second morning to 0.22 grm., and falling again to 0.18 grm., notwithstanding the person had eaten a piece of bread and butter with much salt.

Upon the basis of the above facts we are now enabled to explain the opinion of Barral, who by a series of very accurate analyses, the substance of which was first presented to the French Academy, and subsequently published in a separate form, came to the conclusion that chloride of sodium increased the elimination of the nitrogenised ingredients of the urine. In some of his experiments Barral determined the whole amount of chlorine taken with the food, and, on the other hand, the chlorine and urea excreted. If such a series of analyses were now to be performed by the more accurate methods, there can be no doubt that they would lead to important evidence regarding the causes and influences determining and modifying the amount of chlorine excreted by the kidneys, particularly if the fæces and other excreta were also taken into consideration. There is one way, however, in which chloride of sodium indirectly increases the discharge of urine and its ingredients; namely, by causing thirst when taken in any quantity; the water which is drank in consequence, acting as a stimulant of the kidneys, carries away, not only the salt, but also organic ingredients in solution.

Chlorine of the Urine in Disease.

Since Redtenbacher drew attention to the fact of the absence of the chlorides from the urine discharged by patients in certain stages of pneumonia, and to the diminution of these salts in other stages of that disease, many researches have been made in that direction. Though at first they were mainly directed towards pneumonia, of which disease exclusively the absence of the chlorides was for some time thought to be a peculiar feature,

yet the extension of the investigations to other diseases showed soon that the bearing of the chlorides in all acute diseases was so very much the same, that the idea of its being a peculiarity of pneumonia had to be abandoned.

In all acute febrile diseases the amount of chlorine discharged in the urine sinks rapidly to a minimum, say one-hundredth part of the quantity normal to the individual, until at last, in certain cases, it disappears entirely for a short time. When the diseased action is abating, the amount of the chlorides rises during convalescence, sometimes above the normal average. We have already seen that the total quantity of urine has a similar relation to the stages of acute febrile diseases. Urea, on the other hand, though rising at first in amount inversely to the sinking of the amount of chlorine, afterwards sinks below the healthy average, and during convalescence rises parallel with the amount of chlorine.

In the case of a man suffering from severe pleuro-pneumonia, Vogel found the chlorine sinking rapidly to 0.6 grm. in twenty-four hours on the third day of the disease, to 0.3 grm. on the fourth, on the fifth to almost 0. From this day the diseased action abated, and the appetite improved, when, together with these improvements, the amount of chlorine discharged rose to the normal average, as the following figures show:—0.4, 1.8, 2.6, 5.5, 9.0 grm. From this time the amount of chlorine fluctuated a little, and sometimes exceeded the normal average. It was on the respective days 10.7, 13.5, 9.7, 11.9, 15.9, 10.8 grm.

The same course has been established by the observations of Beale. He found that the chloride of sodium was totally absent from the urine of pneumonic patients at the period of complete hepatisation of the lung, and that it reappeared after the resolution of the inflammation. The fact that the sputa of pneumonic patients contain a very large quantity of the chlorides, must probably be explained by their being in part extravasations and exudations from the blood, which we now know always retains a certain amount of the chlorides. These exudations may either have been deposited at the time when the blood yet possessed an excess of chlorine, or they may have appeared after the chlorine had ceased to be discharged in the urine in appreciable quantities. However, that may ultimately be decided by analysis; what I desire to point out is, that the absence of the chlorides in the urine does not necessarily involve the absence of chlorine from exudations. For the latter are products of diseased action derived directly from stagnant blood, and certainly not subject to the specific laws of secretion. The presence of chlorine in sputa, therefore, at a time when it is absent from the urine, is not sufficient proof of a determination of the chloride towards the inflamed lung; a proposition which, more-

over, loses all probability from the partial or total disappearance from the urine of the chloride in all acute diseases. We may mention bronchitis, typhus, rheumatic fever, pyæmia, pleuritis, as diseases in which this diminution of the chlorides has been observed. We have seen the influence which different quantities of chlorine taken with the food exert upon the amount of chlorine discharged by the urine during health. It is therefore easy to believe that the diet of patients has the greatest influence upon the amount of chlorine in pathological urine; and that the chlorine is diminished or absent because these patients take little or no food, and what they take generally contains no salt. One important point, however, must not be lost sight of, namely, that urine containing no appreciable trace of chlorine is secreted from blood containing a certain amount of it, from which it follows that the composition of the blood is such as not to allow any further removal of chlorine, or that the kidneys have lost their secretory activity as regards chlorine, as well as with reference to water.

The analysis of the amount of chlorine in the urine of patients may, therefore, afford an insight into the degree of the pathological action taking place in the body. A continuous decrease of chlorine in the urine is an indication of the growing severity of the disease, the intensity of which will be greatest when the chlorine in the urine falls to a minimum, say 0.5 grm., or disappears altogether. This may be the combined effect of an entire loss of appetite, copious serous diarrhœa, or other serous exudations, of secretions such as perspirations, and of the want of secreting power of the kidneys. A rise in the amount of chlorine, on the other hand, indicates a steady abatement of the acuteness of the disease, and is a good measure of the returning appetite and improved digestive powers of the patient.

In chronic diseases the excretion of chlorine is generally diminished, correspondingly with the low state of nutrition and moderate appetite of the patients of that class. To this rule, however, diabetes insipidus makes an exception—a disease, during the entire or partial course of which a considerable excess of chlorine is discharged, parallel to the increased amount of other solids. In a case of that description Vogel found the amount of chlorine discharged by the urine so much increased for a period, that on one day it was 29.0 grm. in weight. The same observer found that dropsical patients, when under the influence of diuretics, discharged an increased amount of chlorine, which evidently had passed into the tissues and cavities dissolved in the exudations and transudations. One of these patients discharged 33.0 grm. of chlorine (equal to 55.0 grm. of chloride of sodium), 28.0 grm., and 21 grm. of chlorine, on three successive days, without having taken any more salt than usual with his

food. In these and other chronic cases the amount of chlorine in the urine is a measure of the digestive powers of the patient. A quantity of chlorine, amounting to from 6 to 10 gm. for twenty-four hours, may lead us to infer a good digestion; a quantity of chlorine, however, below 5 gm. for the same time, shows impaired nutrition, provided that the decrease have not been preceded by a diet containing little or no chlorine, or by any of the causes which have been above enumerated, as diminishing the amount of chlorine in the blood, such as serous diarrhœa, exudations, and perspirations. An increase in the amount of chlorine, when not caused by an excessive ingestion with the food, is indicative of diabetes insipidus. In dropsical and hydremic conditions an increase of the amount of chlorine is a favourable symptom.

CHAPTER XXIII.

SULPHURIC ACID AND SULPHATES.

INTRODUCTION.

SULPHURIC acid occurs in the urine in combination partly with alkalies, potassium, and sodium, partly with lime, as gypsum. It has frequently been maintained (first by Proust) that there was a small quantity of sulphur present in urine in such a form that it escaped precipitation by baryum, and as it was mostly obtained by oxydising the residue of urine with nitric, it came to be called unoxydised sulphur. From the researches of Baumann, which I have quoted under the chapters on indigogen, pyrocatechin, and phenol-producing bodies, it is probable, indeed, in the case of the body last mentioned it seems proved, that, at all events in the urine of horses, a certain quantity of sulphur may be present, not indeed in an unoxydised form, but in a form of organic combination of sulphuric acid, whereby this latter acid loses its individual reactive power with baryta, and assumes characters in which its former individuality disappears completely. If any such compounds are present in human urine under ordinary circumstances, they are very small in quantity, as any determination of the quantities of the unprecipitable sulphur in various specimens of urine to be given below will show. There is, however, nothing improbable in the hypothesis that the sulphuric acid of taurocholic acid or taurine, in the moment when it is set free from these compounds, should be recombined with other matters, in the same manner as the glykokoll from the glykocholic acid is combined with a variety of matters.

But even the hypothesis of localising the formation of these organic sulphuric acid compounds, and of the glykokoll compounds in the space of hepatic action, is perhaps too narrow, particularly as Baumann seems to have found that all that is required for the formation of some at least of the sulphuric acid compounds seems to be the presence in the organism of a suitable sulphate and a suitable organic matter.

Mode of Obtaining Sulphates and Sulphuric Acid from Urine.

The sulphates of alkalies and earths can be obtained from urine by evaporation and crystallisation. Gypsum is thus easily

obtained, but sulphate of sodium requires much management and the aid of cold weather. Sulphuric acid can be isolated by precipitants, such as baryum salts; these may then be transformed into alkaline sulphates by fusion with alkaline carbonate; from the solution of these latter the sulphuric acid may be precipitated by lead salts, and the pure lead sulphate may be decomposed by hydrothion. The evaporated solution will leave the sulphuric acid in a pure state.

Mode of Obtaining the Organically Combined Sulphuric Acid and Sulphur from Urine.

When all the precipitable sulphuric acid has been removed by baryum salts, first in alkaline, next in acid solution, the clear filtrate is treated while hot with a current of pure chlorine gas. The organic matter is mostly destroyed, and the sulphuric acid which is set free causes a new precipitate of barytic sulphate with the excess of baryum present from the first operation. Another mode consists in evaporating the urine from which the precipitable sulphuric acid has been removed to dryness, destroying its organic matter with pure nitre, redissolving the fused mass in water and acidifying, when the newly-formed sulphuric acid will remain as a white precipitate combined with some of the excess of baryum contained in the mass. In all these operations the greatest caution is needed to effect a perfect clarification and filtration of all liquids by warming them, letting them stand, and passing them through the densest Swedish filtering paper obtainable. All reagents must be tested for sulphuric acid with great care, and in quantities such as are employed for the operations themselves. Without such precautions the unwary inquirer is likely to be led to snares and delusions.

Mode of Determining the Quantity of Precipitable Sulphuric Acid Present in Urine.

Experience has convinced me that the volumetrical determination of sulphuric acid in urine by baryum salts is an unsafe proceeding, as there is no striking reaction known by which the addition of volumetric fluid to the urine to be tested can be limited with certainty.

The best and safest method of determining sulphuric acid is by precipitation and weighing. 100 c.c., or any measured quantity of filtered urine, are acidulated with some hydrochloric acid, and, by the addition of chloride of baryum in excess, the whole amount of sulphuric acid is precipitated. The precipitate is then boiled for some minutes in the acid fluid, filtered, washed, and exposed to a red heat, the filter being incinerated separately on the cover of the platinum crucible or in a spiral of platinum wire.

To prevent the formation of sulphide of baryum by the reducing influence of any animal matter which may have been intimately mixed with the precipitate, it is advisable to add a little nitric acid to the sulphate in the crucible, after it has got cool from the first heating. It is then again heated for a short time, and, after cooling, may now be weighed.

The formula of the product is BaSO_4 , and it contains 58.79 per cent. Ba.

Quantity of Precipitable Sulphuric Acid Discharged by Healthy Persons during Twenty-Four Hours.

The average amount of sulphuric acid discharged during twenty-four hours by healthy young men fluctuates between 1.5 and 2.5 gm. Vogel and Gruner have made some direct observations of the quantities of sulphuric acid secreted during every single hour of the day, and have found the average of one hour to be 0.09 gm.

The average for every single hour of the forenoon they found 0.06 gm., for one hour of the afternoon 0.1 gm., for one hour of the night 0.07 gm. From this it appears that *the largest amount per hour of sulphuric acid is discharged a few hours after the principal meal of the day. The quantity then begins to decrease, and continues so with every hour up to the principal meal of the next day, after which it again rises.*

In some individuals the discharge of sulphuric acid is effected more rapidly than in others, in whom the total average for the twenty-four hours is spread more equally over that time. The former may have an hourly average varying between 0.317 gm. and 0.016 gm., or between 0.165 gm. and so small a quantity that it cannot be determined.

Physiological Origin of the Precipitable Sulphuric Acid.

Though the analysis of food has shown that a certain amount of sulphuric acid in the form of sulphates is being taken daily, yet this is not sufficient to account for the whole amount discharged by the urine. This excess of sulphuric acid over the amount ingested as such is undoubtedly due to the oxydation in the body of the sulphur which, as we know, enters into the constitution of albuminous substances. As the greater part of our albumen is taken in the form of meat, it is a reasonable supposition that the greater part of the sulphuric acid in the urine of well-living people is due to the oxydation of the sulphur contained in the meat they eat. In accordance with this it has been found that, under a diet consisting principally of meat, the amount of sulphuric acid discharged in the urine may be double or three times the amount of the ordinary average. On the other hand, a purely vegetable diet has been found to make the amount

of sulphuric acid sink considerably below the average under ordinary mixed diet. Lehmann, while living on ordinary mixed food, found 7.026 gm. of sulphuric acid in the urine of twenty-four hours. But when, during twelve successive days, he confined himself to animal food exclusively, the sulphuric acid rose to 10.399 gm. per day. Under an exclusively vegetable diet it fell to 5.846 gm. for twenty-four hours. These quantities are very high, and, like other observations of Lehmann's upon himself, do not permit any conclusion as to the average quantities secreted by other persons. But in itself the experiment is as conclusive as the following ones:—Vogel examined the urine of a person whose ordinary average for twenty-four hours was 2.02 gm. of sulphuric acid. That person took a large supper of meat principally, in consequence of which the discharge of sulphuric acid by the urine rose to 0.5 gm. per hour between midnight and nine o'clock next morning; the ordinary average per hour for that time of the day having been 0.1. During the subsequent twenty-four hours the amount of sulphuric acid rose to 7.3 gm., being more than three times the ordinary average of 2.02 gm. It was observed by Vogel that the rise and fall of the amount of sulphuric acid in the urine of several other persons was mainly dependent upon the amount of sulphur taken with their albuminous food; and that when farinaceous food, containing only a small amount of gluten, such as bread and butter, rice, and similar food, was taken, the amount of sulphuric acid in the urine fell. The same observation was made by Clare, in a series of experiments which he performed upon himself. During three days he lived on meat only, and at the end of those three days he had discharged the respective amounts of sulphuric acid as follows:—On the first day, 2.094 gm.; on the second day, 5.130 gm.; on the third day, 3.868 gm. He then during two days ate common mixed diet, and discharged on the fourth day of the experiment, 3.592 gm.; and on the fifth, 2.262 gm. of sulphuric acid. The next three days he restricted himself to vegetable diet, and discharged on the sixth day of the experiment, 2.262 gm.; on the seventh, 1.394 gm.; on the eighth, 1.022 gm. On the ninth and tenth day he again took his ordinary diet, and secreted 1.979 and 2.859 gm. of sulphuric acid on each day respectively.

These data exhibit quite clearly that the influence of the meat diet showed itself on the second day of the experiment only, in which point the observation differs from that of Vogel, in which the rise in the quantity of sulphuric acid took place already during the night and on the morning following the meat supper. However, this later appearance of the increase is compensated for by its lasting so much longer, that the urine of the fourth day, being the first of the ordinary mixed diet, is yet under the

influence of the meat diet of the previous day, the first day of vegetable diet is yet under the influence of the previous day of mixed diet, and the diminution of the sulphuric acid by the vegetable diet lasts yet over the whole ninth day, when ordinary diet was already taken.

Such are the circumstances on which the amount of sulphuric acid in the urine ordinarily depends. There may, however, be accidental causes which increase the sulphuric acid, and as such must be assigned the internal use of sulphur, sulphurets, sulphuric acid, and sulphates.

The internal use of sulphur has been found by Krause to increase the amount of sulphuric acid in the urine.

It was observed by Boecker and Clare that large doses of red sulphuret of antimony caused a rise in the amount of sulphuric acid in the urine.

The action of the sulphuretted mineral waters, which is generally ascribed to the formation of sulphuric acid in the body, forms an interesting subject for inquiry in this direction.

As to sulphuric acid, it was observed by Vogel that it increased in the urine of a patient who had taken it for the cure of hæmoptisis from 1.2 to 3.0 and 3.28 grammes.

Gruner made some observations regarding the influence of sulphates, and found that sulphate of sodium, when taken internally, caused a considerable increase in the amount of sulphuric acid in the urine. In one experiment the hourly quantity rose from 0.049 grm. to 0.122, 0.176, 0.145, and 0.220 grm. In another experiment the rise was equally well marked, namely, from 0.041 grm. to 0.138, 0.122, and 0.164 grm. The time required by the organism to discharge the excess of sulphuric acid varied in different experiments.

The influences which different physiological conditions of the body may have upon the amount of sulphuric acid in the urine it has not yet been possible to ascertain. We do not know whether the organism requires a certain amount of the sulphates, below which secretion cannot be carried on, or whether sulphates may be retained and accumulated in the economy. According to some experiments of Clare and Gruner, the influences of rest and activity, and of the ingestion of large quantities of water into the stomach, did not appear materially to affect the amount of sulphuric acid in the urine. The prolonged use of sulphates in so-called digestive doses is decidedly weakening, and this depressing action may be due to an accumulation of the salts in the system. When to this it is added that sulphate of sodium in larger doses is an emetic and sulphate of potassium a poison, the question, after the significance of the variations of sulphuric acid and sulphates in the urine, becomes one of sufficient importance to fix the attention of future inquirers.

Quantity of Precipitable Sulphuric Acid in Disease.

The observations hitherto made on this point have not yielded any very decided result. Vogel found sulphuric acid considerably diminished in most acute febrile diseases. As patients suffering from these diseases take little food, and that little mostly of a vegetable nature, the diminution is partly accounted for. The same observer found, however, exceptions to his general rule in three patients affected with violent pneumonia. In these cases the amount of sulphuric acid discharged was considerably above the normal average. The first patient, who was treated with large doses of digitalis, secreted the following quantities of sulphuric acid on nine respective days:—2·4, 3·1, 2·9, 5·7, 4·3, 1·8, 1·1, 1·6, 2·7 grm. Of the two other cases, which took a rapidly fatal turn, the first showed the amount of sulphuric acid to be 2·9 and 1·4 grm. on two respective days, the other on the day of decease, 4·4 grm. On contrasting these figures with those obtained in cases where the amount of sulphuric acid is less, the difference becomes very striking. In a man with diphtheritis buccalis Vogel found only 0·5 grm. of sulphuric acid for the day. In a patient with febrile catarrh it was 0·29 and 0·38 grm. A man affected with pleuritis secreted 0·63 grm. A girl suffering from rheumatic fever discharged 0·8 grm. at the height of the disease, another with erysipelas of the face 0·48 grm.

In chronic diseases Vogel found the amount of sulphuric acid to be variable, but mostly below the normal average; and it remained so in cases where the secretion of chlorides could be vastly increased by administering diuretics, as in cases of dropsy. An increase in the amount of sulphuric acid discharged by patients affected with chronic disease could only be observed after the ingestion into the stomach of sulphuric acid and sulphates, and in diabetic patients after a liberal meal of meat.

Thus a patient labouring under icterus secreted 1·4 grm. of sulphuric acid; a case of rheumatism of the neck gave 1·11; a case of emphysema of the lungs, 1·2 grm. A case of amenorrhœa showed 0·5; of fluor albus, 0·7; of habitual hypermenorrhœa, 0·97 and 1·1 grm. A dropsical patient who, under the influence of diuretics, secreted 33 grm. of chlorine during twenty-four hours, discharged only 1 grm. of sulphuric acid during the same time; and on the day following, with 28 grm. of chlorine, only 0·5 grm. of sulphuric acid. A patient who took sulphuric acid internally, secreted more than 3·0 grm. of it during twenty-four hours, and a patient affected with diabetes insipidus discharged 5·2 grm.

Pathological Indications.

If there can be no doubt about the origin of sulphuric acid, the determination of its quantity in the urine must be useful

for determining the amount of disintegration of albuminous matters in the system, in cases where the ingestion of sulphur in any form or combination is very low or altogether suspended. The amount of sulphuric acid would then, perhaps, correspond in a certain degree with the amount of urea, supposing their inclination to pass the kidneys to be equally great. But upon this point there are yet doubts. Where we find both urea and sulphuric acid in increased quantities, we may be sure that it is due to the oxydation of a large quantity of animal matter introduced into the stomach, to animal or meat diet. A considerable diminution of the quantity of sulphuric acid, on the other hand, indicates that the patient has been taking little or no animal food, little or no vegetable food, or no food at all. Of course, all these features may be constant or accidental. A sudden rise in the amount of sulphuric acid, but of short duration, would, under all circumstances, have to be referred to the ingestion of sulphur in some of its combinations, organic or inorganic.

The relations of sulphuric acid to the processes of the animal economy are by no means simple. Introduced in an organic combination, sulphur becomes oxydized, and in the form of the acid has to join a base. It would, of course, deprive another base of its acid by the right of the stronger. The neutral phosphates are thus most probably deprived of some part of their base.

Sulphuric acid or sulphates are not present in the juices of flesh, as was first ascertained by Berzelius, and afterwards confirmed by Liebig. For the precipitate which baryta causes in the juice is, in many cases, entirely soluble in nitric acid; and if a precipitate of sulphate of baryum remain undissolved, its quantity is so small that it cannot be determined by analysis, even from so large a quantity of flesh as that of an entire fowl or an entire fox.

The use of beef-tea and extract of meat, which increases the secretion of phosphates and chlorides, particularly of potassium, will not directly influence the secretion of sulphates by the urine. The production of sulphuric acid then being apparently confined to the blood, it becomes a question of high importance whether the action of the kidneys does not in part consist in the final oxydation, or that stage of disintegration of albuminous matter in which sulphur, in the form of sulphuric acid, leaves the organic combination, joins a base, and appears in the urine.

Albumen contains 1.6 per cent. of sulphur and 0.4 per cent. of phosphorus. White of eggs contains more sulphur than albumen from blood. Casein contains 0.84 per cent. of sulphur. We may trust soon to know all intermediate stages of matter from albumen down to urea and sulphuric acid, when the analysis of these substances in the urine will be of still greater value than even at present we anticipate.

In horses the ingestion of sulphate also increases the quantity in the urine. Thus in the urine of a horse which on account of colic has been treated with magnesia sulphate, hyposulphite of soda and some aromatics, a deposit of *crystallised gypsum* was observed by Feser and Friedberger ("Zeitschr. f. Pract. Veterinärwissenschaft." Bern, 2 (1874), Nr. 1 and 2, and *ibid.* 3 (1875), p. 11). Here the gypsum was deposited spontaneously from probably acid urine. When to urine of horses, which have had a quantity of sulphate given to them, acetic acid is added, until all carbonate of lime is decomposed and the urine is acid, gypsum in crystals is deposited.

CHAPTER XXIV.

HYPOSULPHUROUS ACID, S_2O_2 , AND SULPHUROUS ACID, SO_2 .

HISTORY AND LITERATURE.

SCHÖNBEIN ("Journ. f. Pract. Chem." 92 (1864), 166) discovered that when normal human urine is treated with amalgamated zinc and sulphuric acid, it evolves hydrothion with the excess of hydrogen produced by the reaction. The same reaction was studied by Sertoli ("Rendic. d. Istitut. Fisiolog. di Pavia," 1869) upon the urine of men, horses, and dogs, and interpreted as belonging to a body which is precipitable by neutral lead acetate, soluble in ammonia, alcohol, and ether, and on being heated to 100° with dilute acids, decomposes, one of its products being hydrothion. These reactions seemed to point to either sulphurous, hyposulphurous, or sulphocyanic acid. Of these hyposulphurous was actually discovered in the urine of dogs and cats by Schmiedeberg ("Archiv. d. Heilk." 1867, p. 422), and the observation was afterwards confirmed by Meissner ("Zeitchr f. Ration. Med." 31 (1868), 322).

Mode of Discovering the Presence of Hyposulphurous Acid in Urine.

The urine is mixed with hydrochloric acid and allowed to stand in a cold place. If it contains hyposulphurous acid, a precipitate of sulphur in a state of fine division will settle, along with some colouring matter and uric acid. This finely-divided sulphur is very soluble, even in alcohol and ether, and must therefore not be washed too much with these agents. It may be dried on a filter and extracted with disulphide of carbon, previously distilled to prove its purity. On evaporation it will leave the sulphur. This is easily recognised by its colour, fusion, and combustion with a blue flame evolving the odour of sulphurous acid. After the decomposition of the hyposulphurous, the urine contains sulphurous acid in solution. The reactions of both acids may therefore be considered together.

Reactions of Hyposulphurous Acid.

It does not exist in the free state, and cannot be distilled. The solutions of its salts give white precipitates with plumbic, mercuric, and argentic salts, which become quickly yellow, brown, and black, particularly on warming, forming sulphides. Stannous chloride yields a brown, mercurous nitrate immediately a black precipitate. Hypochlorite of sodium or chlorine transform the entire amount of sulphur into sulphuric acid, already at the ordinary temperature. Many of these reactions are at times observed in operations upon human urine in a more or less marked manner.

Reactions of Sulphurous Acid.

Sulphurous acid can be distilled unchanged, and is recognisable by its odour. Its neutral salts with alkalies are soluble in water, those of other bases insoluble, but soluble in excess of sulphurous or hydrochloric acid. They are easily transformed into sulphates by heating with concentrated nitric acid, by chlorine, hypochlorous acid, or iodine, no sulphur being precipitated. Baric chloride produces a white pulverulent precipitate in sulphites, which is insoluble in water, but soluble in hydrochloric acid. If hypochlorite of sodium, or chlorate of potassium, or iodine, is added to this solution, sulphate of baryum is immediately deposited. Plumbic acetate precipitates white sulphite, easily soluble in dilute nitric acid. Argentic nitrate gives a white precipitate which on boiling blackens, yielding metal and sulphuric acid. Mercurous nitrate gives a grey precipitate of metallic mercury. Metallic zinc and hydrochloric acid reduce sulphurous acid to hydrothion, which can be shown to be formed by its blackening lead paper.

Mode of Obtaining Hyposulphite of Baryum from Urine of Dogs or Cats.—Schmiedeberg treated the urine of these animals with milk of lime and nitrate of calcium; removed the lime from the filtrate by carbonic acid, neutralised the filtrate with acetic or nitric acid, and precipitated by basic plumbic acetate. The plumbic precipitate he decomposed with ammoniac carbonate, decolorised the solution with animal charcoal, heated it with a sufficiency of caustic baryta to expel all ammonia, precipitated any excess of baryta by carbonic acid, and evaporated the filtrate to crystallisation.

Meissner treated the urine with baryta water in excess, evaporated the filtrate, precipitated it with alcohol, and extracted the precipitate with boiling water. On evaporating the solution and allowing it to cool he obtained hyposulphite of baryum in crystals. This account is, however, extremely doubtful, as no means were employed to separate the mass of urinary salts from the hyposulphite.

Mode of Estimating the Quantity of Sulphur which is Present in Urine in a Form not Sulphuric Acid.

That there was a small quantity of sulphur present in human urine, which could not be precipitated from the acidified liquid by BaCl_2 was first shown by Ronalds ("Phil. Trans." 1847, p. 461). This inquirer determined the precipitable sulphuric acid on the one, and the acid obtainable by oxydation of the residue of urine with nitre on the other hand, and found the amount of sulphur not being sulphuric acid, and which he supposes to have been in organic combination, to have been the following in 5 men in 24 hours each:—(1.) 4.639 grains; (2.) 3.715 gr.; (3.) 4.998 gr.; (4.) 3.866 gr.; (5.) 3.247 gr. Griffiths ("Med. Gaz." March 1848) found 4.0 gr. of sulphur of this kind in the urine of a healthy man, which contained 36 grains of sulphuric acid. When he took some sulphur internally, he passed 76 grains of sulphuric acid, and 7 to 8 grains of sulphur in the other form. After the publication of Sertoli, Löbisch ("Ber. Wien. Akad." 63 (1871, März.) ii.) also estimated the amount of sulphuric acid and of sulphur in the unknown form contained in four specimens of urine. As a preliminary, he removed uric acid by precipitation with acid, which seems a hazardous proceeding, considering his object. He then precipitated the sulphuric acid with BaCl_2 in one portion directly, and in another portion after treatment with potassic chlorate, until chlorine was developed. The difference of sulphuric acid thus obtained from equal quantities of urine gave him the measure for the amount of sulphur not present as sulphuric acid. He found in four experiments with 100 c.c. of urine each, the following quantities of SO_3 , which was precipitable only after oxydation:—(1.) 0.011 grm.; (2.) 0.012 grm.; (3.) 0.009 grm.; (4.) 0.003 grm. He took the mean from his first three observations, without saying why he omitted the fourth, as 0.0104, and assuming a healthy man to excrete 1500 c.c. of urine per day, calculated the amount of sulphur contained in it, in the non-precipitable form, to be represented by 0.156 grm. SO_3 .

Already, before 1870, I had made a great number of determinations of the quantity of this variety of sulphur contained in healthy urine, and in the urine from typhus patients. I removed the sulphuric acid from the urine, partly in alkaline solution, with the baryta mixture employed in Liebig's urea estimation, partly in acid solution; and I then oxydised the non-precipitated sulphur by chlorine gas conducted into the hot mixture. During this operation the urine frequently became orange, then red, next pale, lastly colourless. On heating the white turbidity which had formed became deposited, and was found to be baryum sulphate. The heating must be carried out

cautiously, as little explosions of chloride of nitrogen are apt to occur. In most experiments the product remained flaky for some time, probably from free sulphur (which, in the case of the decomposition of hyposulphites, is always flaky and soft). It is not certain whether all the sulphur is oxydised in this process, or whether some may not escape while the fluid is being treated with chlorine.

The following estimations were made for purposes of comparison :—

Quantitative Experiment.—Total urine of 24 hours. 1080 c.c. It was divided in three parts of 360 c.c. each (A), (B), (C), which were treated as follows :—

(A) was treated with chlorine gas, precipitated by BaCl_2 , to get total H_2SO_4 from sulphate and unknown sulphur compounds. It amounted to 2.0270 grm.

(B) was treated with HCl , precipitated with BaCl_2 , which gave precipitate (a). The filtrate was heated with Cl , and gave precipitate (b).

$$\begin{array}{r} (a) = 1.9880 \text{ grm. BaSO}_4 \\ (b) = 0.1730 \text{ " " } \end{array}$$

$$\text{Total, } 2.1610 \text{ " "}$$

(C) was treated with Liebig's baryta solution. The washed precipitate was extracted with HCl , to separate phosphate. The insoluble part was (a), and the solution treated with Cl gave (b).

$$\begin{array}{r} (a) = 1.8480 \text{ grm. BaSO}_4 \\ (b) = 0.2060 \text{ " " } \end{array}$$

$$\text{Total, } 2.0540 \text{ " "}$$

Total sulphur in the unknown form in 1080 c.c. = 0.07128 grm., assuming minimum of 3×0.1730 grm. sulphate. If 100 grm. dry albumen contain 1.6 grm. S, then 0.07128 grm. S represent 4.44 grm. dry albumen.

Experiments upon Urine, mixed with Sulphuric Acid, by which Sulphurous Acid is Obtained in the Distillates.

Urine (500 c.c.) was mixed with one-eighth of its weight of concentrated sulphuric acid and distilled. It was evident from the change of colour that this acid effected a much greater chemolytic action than the acids, oxalic and phosphoric, employed in some former experiments.

The first 50 c.c. of distillate which passed over contained neither sulphuric nor sulphurous acid. The subsequent distillates all contained *sulphurous acid*. For the identification of this acid three reactions were relied upon.

1. Nitric acid and baryum chloride *quickly* gave a deposit of baryum sulphate. The latter was analysed by fusion in potash, and subsequent determination of the baryum and sulphuric acid.

2. Iodate of potassium, hydrochloric acid, and starch solution, all dilute, produced an almost immediate *blue precipitate of iodide of starch*, due to the reduction of the iodic acid by the sulphurous.

3. Metallic zinc (previously proved to be free from sulphur) and hydrochloric acid when added to the distillate produced an immediate evolution of sulphuretted hydrogen, which coloured lead paper black.

These tests are diagnostic of sulphurous acid; sulphocyanic acid, which also yields these tests, being excluded by the absence of the colour reaction with ferric chloride; other tests were, however, also tried, and all gave affirmative evidence.

Sulphurous Acid in the Distillates from Extracts of Urine.

The extracts of urine described under the chapters on urochrome and its products, were decomposed with concentrated sulphuric acid and subjected to distillation. These distillates always contained considerable quantities of *acetic* and *formic* acid (12th Rep. of the Med. Officer of the Privy Council, 1870; Appendix Nr. 12, p. 274), besides *benzoic acid*, and an *oil*. The baryum salt of acetic and formic acid were purified by crystallisation. The mother-liquors regularly contained a quantity of *sulphurous acid*, easily identified by nitric acid and boiling, or by iodic acid and starch, or by zinc and hydrochloric acid. The distillates never contained any sulphuretted hydrogen, no prussic acid, and no sulphocyanic acid. But they always contained some *nitrous acid*. In the baryta salts the reaction for sulphurous acid was soon lost, and iodic acid failed to give any reaction with starch. But now potassic iodide with starch and sulphuric acid gave a blue reaction. I preserve a quantity of 53 grm. of baryum salt, every pinch of which now gives this reaction for nitrous acid, as formerly it gave that for sulphurous acid. Therefore both Lehmann and Bence Jones seem to have been correct in part in their controversy, Bence Jones by maintaining the presence of nitrous acid in these distillates, Lehmann that of sulphurous acid; but each was somewhat in error, Bence Jones by overlooking the sulphurous acid, Lehmann by denying the nitrous.

CHAPTER XXV.

HYDROTHION, H_2S , AND HYDRO-SULPHOCYANIC ACID, CNSH .

INTRODUCTION.

HYDROTHION has been found in urine under different circumstances, the most common being a state of decomposition engendered in the urine by disease of the bladder or neighbouring organs. In these cases the urine is mostly alkaline. Neubauer, however, observed the case of a man who was gouty and paralysed in both legs, and discharged periodically urine which was feebly acid, light yellow, formed a sediment, and blackened immediately a piece of paper soaked with lead acetate held above it.

The volatility, the smell, and the power to blacken lead paper characterise hydrosulphuric acid sufficiently. The determination of its quantity can be effected by expelling it by heat, and passing it through arsenious acid, and weighing the yellow sulphide formed.

Treviranus found that saliva gave a red coloration with ferric chloride. That this was due to *hydro-sulphocyanic acid* was discovered by Tiedemann and Gmelin ("Die Verdauung," etc. 1 (1826), 22). They believed it to be present as potassium or sodium compound. Leared ("Proceed. Royal Soc." 16 (1870), 18) then discovered a number of reactions upon blood and urine, from which he concluded that these liquids normally contained sulphocyanides. This view, as regards the urine, has lately been supported by Gscheidlen (Pflüger's "Archiv." 14 (1876), 401). He removed the sulphates and phosphates by baryta, evaporated the filtrate to a syrup, extracted with alcohol, evaporated the alcohol, dissolved the residue in water, decolorised the solution with a little animal charcoal, and added ferric chloride to the filtrate. The intensely red colour produced indicated sulphocyanide. He obtained this result not only with human urine, but also with the urine of horses, horned cattle, dogs, cats, and rabbits.

He next concentrated urine, removed sulphates and phosphates

by baryta, and distilled the filtrate with phosphoric acid. The distillate was received over lead carbonate, which became black from hydrothion. The lead was extracted with water and alcohol, both boiling, and the insoluble residue was treated with sodic carbonate, to decompose any insoluble sulphocyanide of lead. The filtrate was evaporated to dryness, extracted with alcohol, and the residue, after evaporation of the alcohol, was strongly reddened by ferric chloride. Extracts thus made all yield hydrothion, with zinc and hydrochloric acid, and thus afford some further information on the reaction discovered by Schönbein, and studied further by Sertoli and Löbisch, as stated in the previous chapter. The body which yields hydrothion is soluble in alcohol; the part insoluble in alcohol no longer yields hydrothion. The alkaline sulphocyanides are soluble in alcohol.

An alcoholic extract thus made from fourteen litres of human urine was treated with milk of lime, and thereby somewhat decolorised. The filtrate was again evaporated, and extracted a second time with alcohol. This was evaporated, and the residue dissolved in water. This solution was divided in forty equal parts, each part was mixed with neutral lead acetate in necessary quantity, and immediately filtered. The filtrates were united and warmed in the water-bath. After a short time they deposited a slightly yellow crystalline heavy powder, which was boiled with distilled water (!), dried, and weighed. It amounted to 0.1381 gm. It was placed into a small beaker and warmed with nitric acid on the water-bath, and yielded 0.1221 gm. lead sulphate dried at 100°. This quantity corresponds to 0.373 gm. lead sulphocyanide. These quantitative proportions seem the only proof which Gscheidlen gives of the first precipitate having been sulphocyanide at all. The cardinal proof of the presence of the nitrogen is wanting.

Voit ("Zeitschr. f. Biolog." 1 (1865), 127, 129, and 149) found a body in urine which contained nitrogen, gave a compound with mercuric nitrate which was easily decomposed; and when heated in a silver dish with either lime water or caustic potash, covered the silver with a black layer of sulphide, and evolved ammonia. All these reactions are exhibited by sulphocyanides. The mercuric nitrate can be used to separate the body from urine. The precipitate (as obtained in Liebig's urea determination) is decomposed with hydrothion, the filtrate neutralised with soda, evaporated to dryness and extracted with alcohol. The residue from this extract dissolved in a little water gives the red test with ferric chloride. Gscheidlen estimated the amount of sulphocyanic acid in human urine to be about 0.0225 gm. in one litre, equal to 0.0314 sodic, or 0.0376 potassic sulphocyanide. The estimate was made by comparing the ferric colorations of the

specimens of urine with coloured sulphocyanide of iron solution of known strength. The largest proportion of sulphocyanogen seems to occur in the urine some hours after the principal meal of the day. Gscheidlen ascribes this to the salivary function. When in a dog he diverted all the saliva, by cutting the ducts and inserting canulae, sulphocyanogen no longer appeared in the urine. The pancreatic secretion and the chyle contain, according to Lehmann ("Zoochemie," 1858, p. 79 and 221), no sulphocyanide, and are not coloured red by ferric chloride. I have disproved all statements of Gscheidlen in a paper published in Pflüger's "Archiv." while this sheet was going through the press.

Note on Sulphocyanide of Lead.—Gscheidlen has relied on the statement of handbooks that plumbic sulphocyanide was insoluble in cold water, and assumed that it was also insoluble in, and not changed by hot. All these and other data concerning this salt to be found in text-books are incorrect. Plumbic sulphocyanide is white, not yellow; it is little soluble in cold, more soluble in boiling water, and deposits from this on cooling, in splendid white crystals; it is therefore not the fact that by boiling with water it is decomposed into an unknown yellow or insoluble salt, and an acid liquid of obscure properties. The warm solution of pure plumbic sulphocyanide in water, with sulphuric acid and ferric chloride, gives the red test; it also gives a blue reaction with potassic iodate, sulphuric acid and starch, a reaction, and hitherto believed to be diagnostic of sulphurous acid.

Physiological Considerations Suggested by the Different Forms in which Sulphur appears in the Urine.

The sulphur compounds besides sulphuric acid, in salts or organic combinations which have as yet been found in urine, whether of man or animals, are :—Hyposulphurous and sulphurous acid; sulphocyanic acid (alleged by Gscheidlen and Leared, not found by Gorup-Besanez and myself); hydrothion; taurocholic acid; taurine; cystine; tauro-carbamic acid. Of these only the three first acids and cystine evolve hydrothion with HCl and zinc, the other substances do not. From this circumstance Kulz draws the conclusion, that as hyposulphurous acid and cystine have not been found in human urine, while according to him sulphocyanic acid can be easily proved to be present, the development of H_2S by HCl and Zn, must be due to the presence of sulphocyanic acid.

The bearing of taurine when introduced into the stomach of men and animals with ordinary food has been examined by E. Salkowsky ("Ber. Deutsch. Chem." G. v. Heft 13). In men the taurine is excreted by the kidneys as tauro-carbamic acid, $C_3H_8N_2SO_4$, an acid, the potassium salt of which can be produced

by allowing a mixture of taurine and potassic cyanate first to deliquesce and then to crystallise, by then decomposing the salt with sulphuric acid and crystallising the acid from alcohol; as much as 15 grms. consumed in three days were almost completely recovered from the urine in this shape. But when the taurine is given to rabbits with other food, only one quarter remains unattacked, and reappears in the urine as taurine; a second quarter of the sulphur appears in the urine as hyposulphurous acid, and about half the sulphur appears as sulphuric acid. By injecting the necessary quantities of taurine solution into the stomach of rabbits, the average amount of sulphuric acid present in their urine could be increased to four and five fold. As rabbits die under the influence of this treatment continued for some time, it is possible that they perish partly from the removal of such quantities of alkali as are required by the excessive amount of acid formed. The details of the proceedings regarding taurine E. Salkowsky has given in Virchow's "Archiv." 58, 460. The presence of hyposulphurous acid he determined as follows:—The urine was precipitated with milk of lime; filtered, neutralised with carbonic acid gas, filtered again, and precipitated with basic lead acetate. The precipitate was used for finding the hyposulphurous acid, the filtrate for the taurine. From the lead precipitate the hyposulphurous acid was isolated by the process of Schmiedeberg; or the urine of rabbits was mixed with hydrochloric acid, which caused the liquid to show an opalescence at first, and then the sulphur coalesced and was deposited. The solution and deposit yielded to chloroform all the sulphur which was obtained in crystals from the solvent. The sulphurous acid formed at the same time he isolated by distilling the urine with sulphuric acid. The condensing tube always exhibited a dew of sulphur, and the distillate always contained sulphurous acid, if the rabbit had digested taurine; normal rabbit's urine never showed any trace of either. Salkowsky supposes that all sulphur present in rabbit's urine which is not there as sulphuric is present as hyposulphurous acid, and proposes to calculate the difference between fully oxydised precipitable and not fully oxydised sulphur, obtainable as sulphuric acid by fusion with nitre, as hyposulphurous only. The results obtained by Baumann make this proposal inadmissible, while the results of E. Salkowsky show that Baumann's assumption that all non-precipitable sulphur is present in the form of the organic compounds adduced by him is also inadmissible. And ultimately E. Salkowsky comes in conflict with himself, when he says in one place that all not fully oxydised sulphur in rabbit's urine is present as hyposulphurous acid; in another place, that normal rabbit's urine never shows any hyposulphurous acid; and in a third, that the urine

of rabbits fed upon potatoes contains regularly, besides sulphuric acid, another sulphurised organic body, containing "neutral" sulphur to the amount of 1 out of 5 parts contained in the urine.

When dogs are made to consume taurine with their food, no hyposulphurous acid is formed as in the rabbit, but the taurine is excreted partly or entirely as tauro-carbamic acid.

From researches, which are in progress in my laboratory while this sheet is passing through the press, it appears that the problematical sulphur compound contained in urine is an alkaloid, which yields all the reactions in connection with sulphur alluded to in the foregoing, and on decomposition by chemolytic agents, furnishes free sulphur and sulphurous acid.

CHAPTER XXVI.

PHOSPHORIC ACID AND PHOSPHATES.

OCCURRENCE.

PHOSPHORUS occurs in organised beings only in one form, that of so-called ortho-phosphoric acid. But this is variously combined, partly with bases, lime, magnesia, potash, soda, or ammonia, in which salts the phosphoric acid can be found by direct reagents; partly with organic compounds, particularly glycerine, fatty acids, and basic bodies, in such a manner that the presence of the phosphoric acid cannot be recognised by its ordinary tests before the organic matter has been destroyed. Compounds of the latter class occur in large quantities in the brain and nerve marrow, and are also present in the blood, and all liquids and tissues containing cells, including the male sperma and the pus of abscesses and wounds. In the urine, however, phosphorus has as yet been shown to occur in one form only, namely, that of the oxygen acid combined with the bases above mentioned.

Physical and Chemical Properties.

Phosphoric acid, $P_2O_5 \cdot 3H_2O$, may be obtained in crystals forming quadrangular or hexagonal prisms, transparent-like glass, or as a syrupy liquid. When heated to 160° it begins to lose water, and at a temperature of 213° is transformed into pyrophosphoric acid, $P_2O_5 \cdot 2H_2O$, or $H_4P_2O_7$. When heated still more it loses another molecule of water, and is then metaphosphoric acid, $P_2O_5 \cdot H_2O$, or $HOPO_3$. When exposed to red heat in an open platinum dish it first becomes anhydrous, and is then slowly volatilised. It is easily soluble in water and alcohol, and its solutions exhibit a strongly acid reaction. Solutions of albumen, chloride of baryum or calcium, do not cause any precipitate in a solution of phosphoric acid; the solutions of caustic baryta, strontia or lime, when added in excess, produce a white precipitate. Phosphoric acid has great affinity for the basic oxydes, and forms with them the phosphates, which may contain in the simple molecule H_3PO_4 one, two, or three atoms of any of the monodynamic, or in a double molecule, $H_6P_2O_8$, one, two, or three atoms of any of the didynamic metals, and so on, one

dynamicity of an atom of any metal capable of entering at all into combination replacing one atom of hydrogen either in the single or double molecule of the acid.

Decompositions.

Phosphoric acid, when heated with charcoal, is reduced, and evolves phosphorus, which burns again on coming in contact with air. When the heating is carried on in a retort, the mouth of which dips into water, the phosphorus can be collected, as it sinks in the water and is not decomposed. Before the discovery of phosphorus in bones, all phosphorus was made from urinary salts only, which, owing to the considerable amount of organic matter present with them, do not require the addition of charcoal; it was by the simple calcination of urinary salts in retorts that Kunkel first discovered this remarkable body.

Compounds.

Phosphates of Alkali Metals.—Phosphate with two atoms of sodium and one of hydrogen, so-called alkaline phosphate, HNa_2PO_4 , may occur abnormally in the alkaline urine of chlorosis. Ammonio phosphate of sodium, $\text{HNa}(\text{NH}_4)\text{PO}_4 + 4\text{H}_2\text{O}$, may be obtained from urine in crystals. Acid phosphate of sodium, H_2NaPO_4 , may also be obtained from fresh acid urine in crystals.

Phosphates of Mixed Alkali and Earth Metals.—Of these we are principally interested in the ammonio phosphate of magnesium, $\text{Mg}(\text{NH}_4)\text{PO}_4 + 6\text{H}_2\text{O}$, which always forms when magnesian phosphate meets with ammonia in excess.

Phosphates of Alkaline Earth Metals.—The acid phosphate of calcium, CaHPO_4 , represents the so-called soluble bone-earth. To this the acid phosphate of magnesium, MgHPO_4 , is analogous. Of the foregoing three classes of salts, the phosphates of the alkalies are easily soluble in water, the others are scarcely soluble, or altogether insoluble. They all dissolve in nitric or hydrochloric acid. The phosphates of the alkaline earths, when newly precipitated, are, moreover, soluble in acetic acid. The solution of an earthy phosphate in an acid, when neutralised with an alkali, throws down a precipitate of the original phosphate, which is to a considerable extent soluble in an excess of the alkali if the latter be concentrated. The insoluble phosphates are, as a rule, soluble to a certain extent in an excess of a solution of any salt, from which they have been precipitated by phosphate of sodium; this solution becomes turbid on heating, and clears again on cooling.

With the common soluble phosphates, nitrate of silver produces a yellow precipitate, Ag_3PO_4 , which is soluble in nitric acid, and in ammonia. Acetate of lead produces a white precipitate

$\text{Pb}_3\text{P}_2\text{O}_8$, which is soluble in nitric acid, but insoluble in acetic acid and in ammonia. If chlorides are present, the precipitate contains chloride of lead in chemical combination.

Chloride of baryum and chloride of calcium produce white precipitates with the soluble phosphates, $\text{Ba}_3\text{P}_2\text{O}_8$ and $\text{Ca}_3\text{P}_2\text{O}_8$, each, while fresh, readily soluble in hydrochloric, nitric, or acetic acid.

When a solution of phosphate of calcium in acetic acid is allowed to stand some time, the phosphate has a great inclination to fall down from this solution in a crystalline state, particularly when the mixture is warmed a little, and when the phosphate is prevalent. Phosphate of calcium is somewhat soluble in water containing carbonic acid, and in salts of ammonium, even when free ammonia is present. From its solution in acetic acid, or from its solution in hydrochloric acid when mixed with acetate of sodium (which is virtually a solution in acetic acid, because hydrochloric acid, combining with the sodium, sets acetic acid free, which is now the solvent for the phosphate of calcium), oxalate of ammonium throws down the whole amount of calcium as oxalate of calcium. From its solution in hydrochloric or nitric acid, the entire amount of calcium may be precipitated by means of sulphuric acid and alcohol. These reactions are the bases for the quantitative determination of calcium in ashes and the earth of bones.

A mixture of sulphate of magnesium or chloride of magnesium, with chloride of ammonium and ammonia, produces a crystalline precipitate in soluble phosphates, which has the composition $\text{Mg}(\text{NH}_4)\text{PO}_4 + 6\text{H}_2\text{O}$, is easily soluble in all acids, somewhat soluble in pure water, and perfectly insoluble in water containing ammonia, even if a large amount of any salt of ammonium should be present. This precipitate, after exposure to red heat, is of the composition $\text{Mg}_2\text{P}_2\text{O}_7$, and is the qualitative and quantitative test for phosphoric acid (in absence of arsenic acid) in all combinations which are soluble in water, the watery solution of which does, however, not become turbid by admixture of a solution of chloride of ammonium and ammonia. In very dilute solutions the precipitate forms only slowly. When the solution contains tartaric acid and oxide of iron, some tartrate of magnesium and oxide of iron may easily be mixed with the precipitate.

Chloride of iron produces in solutions of phosphates a yellowish-white precipitate, which is soluble in hydrochloric acid, in an excess of chloride of iron, in acetate of iron, and in ammonia. This precipitate is, however, quite insoluble in acetic acid, and will, for this reason, form even when its solution in hydrochloric acid is mixed with acetate of sodium, as already

explained, or when the solution in hydrochloric acid of the phosphate of an alkaline earth metal is mixed with a small quantity of chloride of iron, and with acetate of sodium. If the solution of any phosphate in hydrochloric acid, after any excess of the acid has been neutralised by a little ammonia or carbonate of sodium, is mixed first with acetate of sodium, and then with chloride of iron in slight excess (which may be recognised by the fluid assuming a reddish colour), and is then heated to ebullition, a reddish-brown precipitate is obtained, which contains the whole amount of oxyde of iron and all the phosphoric acid present. It is filtered hot, and the precipitate and filter are washed with hot water. This test forms the basis of the method for removing all phosphoric acid and iron from solutions in which the quantity of calcium and magnesium and isomorphous metals has yet to be determined.

On mixing a solution of the nitrate of oxyde of mercury with a solution of phosphate of sodium, a white flocculent precipitate of phosphate of oxyde of mercury is immediately produced, which, on being allowed to stand in the fluid, rapidly becomes crystalline. A solution of corrosive sublimate, however, may be mixed with the alkaline phosphate without any turbidity being produced. If to a mixture of the two first-mentioned salts we add a solution of chloride of sodium before the precipitate has had time to become crystalline, the latter will immediately decompose with the chloride of sodium, corrosive sublimate and phosphate of sodium being produced: the precipitate disappears, and the fluid becomes perfectly clear.

This test is the basis of the method for ascertaining the amount of oxyde of mercury contained in a solution of its nitrate.

A very accurate test for showing the presence of minute quantities of phosphoric acid is molybdate of ammonium. The liquid to be tested is strongly acidified with nitric acid, and then molybdate of ammonium, previously strongly acidified with nitric acid, is added. If phosphoric acid is present in the mixture in any quantity, an immediate yellow precipitate ensues. If only traces are present the liquid becomes yellow. Heating in both cases accelerates the reaction, and rubbing of the walls of the glass vessel with a glass rod facilitates the deposition of small amounts of the yellow compound. The yellow compound contains phosphoric acid, ammonia, and about thirty-two molecules of molybdic acid, so that the reason for having a great excess of molybdic acid present in the reagent solution is explained by the composition of the precipitate. If accurately made the precipitate may be used for the determination of either ammonia or phosphoric acid directly by weighing it and calculating their quantity. But as the urine contains other alkaloids precipitabl

by phospho-molybdic acid, a precipitate obtained from urine by this reaction, without previous incineration, might contain slight impurities, and it is therefore preferable to dissolve it in ammonia, and precipitate the phosphoric acid by magnesia mixture in the manner to be described lower down.

Volumetric Estimation of Phosphoric Acid in Urine by means of Uranium Salts.

When to a hot solution of any soluble phosphate containing free acetic acid a solution of acetate or nitrate of uranium is added, a whitish-yellow precipitate of uranium phosphate is immediately produced. This consists of 19.91 per cent. of P_2O_5 and 80.09 per cent. U_2O_5 . When the uranium salt is added in slight excess, or until a filtered portion exhibits a reddish-brown colour or precipitate with ferrocyanide of potassium, all phosphoric acid is precipitated. The precipitate of uranium phosphate is unchangeable in its fluid, and does not transform into a basic combination like the phosphate of iron. For this reason it is perhaps a more certain means of determining phosphoric acid in urine than the corresponding iron salt formerly used.

Preparation of the Standard Solutions.

(a) *Phosphate of Sodium Solution.*—Transparent, dry but not withered, crystals of common phosphate of sodium are powdered, and 10.085 grm. weighed off; they are then dissolved in sufficient water to make up 1 litre; 50 c.c. of this solution contain 0.1 grm. P_2O_5 .

(b) *Acetate of Sodium Solution.*—100 grm. acetate of sodium, and 50 c.c. of dilute acetic acid are dissolved in sufficient water to make up 1 litre.

(c) *Solution of Uranium.*—A quantity of uranium oxyde, or of the yellow urano-sodic carbonate is dissolved in acetic acid, and the strength of the solution ascertained by means of the phosphate of sodium solution (a). The solution is next to be so diluted that the application of 1 c.c. indicates the precipitation of 5 milligram. of phosphoric acid, or 50 c.c. of the sodium-phosphate solution are to be exactly precipitated by 20 c.c. of the uranium acetate solution, and there is yet to be a slight excess of uranium solution in the fluid to give the test with ferrocyanide. To effect this 50 c.c. of the phosphate solution (a) are mixed with 5 c.c. of the sodium acetate solution (b), and heated in a water-bath to near boiling. The uranium solution of unknown strength is now added slowly and cautiously, until a few drops of the mixture filtered through paper produce a distinct reddish-brown reaction with solution of ferrocyanide of potassium on white paper. Supposing that to this point 15 c.c. of the uranium solution had been used, then the solution would

yet be too strong, and would have to be diluted with one quarter of its volume of water in order to be of the required strength, and thus other degrees in proportion. The standard solution of uranium should contain 20.3 grm. U_2O_5 in each litre.

Application to the Urine.

Determination of the whole amount of phosphoric acid. To 50 c.c. of filtered urine 5 c.c. of the acetate solution (b) are given, and while the mixture is heated in a water-bath, the uranium solution is allowed to drop in from a burette. When the precipitate is not visibly increased, the fluid is tested by filtering a drop or two through a piece of blotting paper, which is closely pressed upon a paper soaked with solution of ferrocyanide. If no reaction ensues more uranium solution has to be added. As soon, however, as a reddish-brown reaction appears, the precipitation is complete. Every c.c. of uranium solution used indicates 5 milligram. of phosphoric acid precipitated.

Separation of Phosphoric Acid Combined with Earths, from the Portion Combined with Alkali Metals.

To effect this the operator may dissolve the precipitated phosphates of earths in acetic acid, and determine the phosphoric acid in this solution. He will then deduct the quantity found in this last operation from the total quantity of phosphoric acid present in the urine, when the difference will give him the phosphoric acid in combination with alkalies.

Determination of Phosphoric Acid by Precipitation and Weighing of the Precipitate.

A measured quantity of urine is treated with nitric acid in excess, and to the mixture molybdate of ammonium is added, until it produces no further precipitate; the mixture is heated until it is clear, and all precipitate is deposited as a yellow powder. This is collected on a filter and washed and dissolved in ammonia; magnesia mixture is now added, the mixture stirred, the glass rubbed with the glass rod, and the mixture allowed to stand over night. The precipitated ammonio-phosphate of magnesia is collected, dried, and ignited, and from the quantity of pyrophosphate obtained that of the phosphoric acid is calculated.

Quantity of Phosphoric Acid Discharged by Healthy Persons during Twenty-Four Hours.

The results of numerous examinations are arranged in the following table, which gives, after the name of the observer, the average quantities of acid found in single individuals,

and the average of all examinations of each observer at the end:—

Breed, average of four individuals, . . .	5.180 grm. to 3.765
Winter, first individual, 3.7; second, 4.2; third, 5.2	
grm.	average 4.36
Mosler, first series, 2.4; second series, 3.7 in the same	
individual,	average 3.05
Neubauer, first individual, 3.1; second, 1.6, . . .	average 2.35
Aubert,	2.8
Average amount of P_2O_5 discharged by an adult male in	
twenty-four hours,	3.66
Ditto in one hour	0.15

According to the observations of Winter, 100 kilogrm. of man discharge on an average of 0.27 grm. and 100 centimetres 0.1 grm. of phosphoric acid.

The maximum and minimum amount of phosphoric acid discharged by single individuals during twenty-four hours is subject to considerable variations, as exhibited by the following observations:—

	Maximum.	Minimum.
Neubauer found in one individual daily	2.16 gr.	1.21 gr.
" found in second individual . . .	4.88 gr.	2.44 gr.
Mosler, ditto	4.86 gr.	2.40 gr.

The fluctuations in the hourly average are still greater, so that Vogel found by a series of experiments the maximum to be 0.216, while the minimum of the same subject only amounted to 0.085 grm. Both extremes happened on one and the same day, the whole inquiry extending over ten days.

Through the observations of Winter, Mosler, and Vogel it has been established that the rise and fall in the hourly amount of phosphoric acid is a regular one during each twenty-four hours, the rise invariably taking place soon after the principal meal of the day, which was taken at noon. The maximum secretion was observed during the hours of the evening; the quantity fell during the night, and was at the lowest ebb during the morning. These fluctuations are well illustrated by the following table given by Vogel:—

Table showing the Amount of Phosphoric Acid secreted by four Individuals during one hour of the night, afternoon, and forenoon.

Individuals.	Afternoon.	Night.	Forenoon.
A.	0.18	0.20	0.13
B.	0.28	0.21	0.11
C.	0.18	0.16	0.10
D.	0.11	0.14	0.11

This table shows that different persons discharge the phosphorus taken with their food at different periods after the ingestion, some more quickly, others more slowly; in some the process is spread over a longer period of time than in others. Thus B. discharged the greater part of the phosphorus taken with his dinner soon after it; the secretion of phosphoric acid reached its climax in the afternoon, and fell during the night and following morning until the next principal meal. The difference between the hours before the meal and after it is here greatest. In C. the climax of the secretion falls more towards the evening, and there is less difference between afternoon and night. In D. the maximum hourly average is in the night; and probably his digestion was much slower than that of the other three persons, though all four took their dinners at one and the same time, namely, 1 P.M.

Physiology of Phosphoric Acid in the Urine.

The introduction into the body of phosphorus, either in the form of the acid, or of phosphates, or in combination with albuminous substances, such as eggs, brains, &c., gives rise to an increase of the acid in the urine.

Total abstinence from food, or from food containing phosphorus, on the other hand, diminishes the amount of phosphoric acid in the urine. Total abstinence will, however, not cause the entire disappearance from the urine of phosphates, as has been observed with regard to chloride of sodium. This is, perhaps, partly due to the continued oxydation of albuminous substances. Aubert observed the urine of a person to contain 2·8 grammes per day under ordinary circumstances. This person took 31 grammes of phosphate of soda, whereupon the amount of phosphoric acid in the urine rose to 4·1 grammes for twenty-four hours. When abstaining from food, Mosler found phosphoric acid to sink to half the ordinary quantity; when he took large meals of albuminous substances, the amount of the acid became doubled in consequence.

But the excretion of phosphoric acid is not exclusively dependent upon the quantities introduced. A series of observations demonstrate that the same influences which govern the excretion of chlorine and sulphuric acid are active in the excretion of phosphoric acid. Different degrees or morbid changes of the secretory activity of the kidneys, actual disease of the kidneys, changes in the mode of disintegration of matter in the organism, must be looked to as causes of the variation of the amount of phosphoric acid. The drinking of large quantities of water causes an increase in the amount of phosphoric acid beyond the quantity introduced with the water, which can only be explained by an increased production in the body of phosphoric acid, by

changes which make an increased amount of phosphates available for excretion, and by a stimulated activity of the kidneys. The organism may at one time contain an excess of phosphoric acid, at other times the acid may be deficient, it will, however, be difficult fully to establish these points, until the normal amount of phosphoric acid contained in all parts of the body and its changes and variations within the range of perfect health be known. And then the examinations will have to comprise a complete analysis of all food, and of all excretions.

Quantity of Phosphoric Acid in the Urine of Disease.

In acute but not very severe diseases the amount of phosphoric acid in the urine decreases at first most probably in consequence of the low diet, and afterwards rises again with a more liberal allowance of food. During convalescence the normal amount is sometimes exceeded in consequence of an increased quantity of food.

If the illness, though combined with violent fever, only lasts a short time, the decrease of the amount of phosphoric acid is sometimes very slight and scarcely perceptible.

The following data have been collected mainly by Vogel :—

Males.—1. A young man, affected by a severe febrile angina tonsillaris, discharged 2·8 grammes of phosphoric acid on the day of his reception into the hospital. He had an emetic given to him, which caused violent vomiting. This was followed by low diet. On the second day the amount of phosphoric acid had fallen to 1·7 grm. He now improved, and had quarter diet. The two following days showed 2·6 and 2·5 grm. of phosphoric acid respectively. He now was placed upon half diet; and on the following day the P_2O_5 rose to 3·2 grm. He recovered, and was discharged.

2. Pneumonia, not very severe. The patient was discharged after eight days. The daily amounts of P_2O_5 were 2·4, 2·5, 2·9, 2·4, and 2·3 grm.

3. Pneumonia, more severe. During the acme of the disease, the daily amounts of phosphoric acid were 1·7, 0·8, 2·1, 1·2, 0·9, 2·1, 1·9, 1·1 grm.

4. Pneumonia, similarly severe, 1·6, 1·4, 2·2, 2·3, 1·6 grm.

5. Febrile bronchial catarrh, 1·4, 1·5, 1·7, 1·5, 2·8 grm.

6. Convalescence from severe pneumonia, 3·8, 2·7, 3·2, 3·5 grm., 3·9, 1·8, 2·5, &c.

7. Similar case, 1·9, 5·6, 2·8, 1·5, 3·2, 2·8 grm.

8. Convalescence from severe bronchial catarrh, 4·8 grm.

9. Catarrh of the organs of digestion, with eczema and violent fever. The case took a rapid course, so that the patient was dismissed cured after eight days. The amount of P_2O_5 was 2·3, 2·6, 2·7, 2·6, 3·4 grm.

Females.—1. Rheumatic fever, 2·1, 2·3, 2·2 grm.

2. Catarrh of the stomach, 1·1, 1·2 grm.

3. Catarrhal fever, acme of the disease, 1·6 grm.

4. Convalescence from typhus, 5·2 grm.

When the diseases are of a more severe nature, so as to cause a long abstinence from food, or to take a fatal turn, the decrease of phosphoric acid in the urine becomes much more considerable.

Thus, a girl with severe febrile catarrh of the lungs discharged, during the acme of the disease, 0·7, 0·5 grm. of phosphoric acid; during convalescence it rose to 1·3 and 2·5 grm.

Fatal end of acute tuberculosis of lungs, 0·4, 0·4, 0·3, 0·3, 0·2, 0·1, 0·08 grm. (day of decease).

Gangrene of the lungs, fatal issue, 3·0, 2·5, 2·20, 0·7 grm.

In some exceptional cases the amount of phosphoric acid discharged during the height of acute diseases may considerably exceed the amount discharged during health.

A man of middle age suffered from pneumonia, and was treated with large doses of digitalis, cured and discharged, 4·3, 5·1, 4·1, 8·4, 7·9, 4·5, 2·9, 5·0 grm.

In chronic diseases the excretion of phosphoric acid takes a very irregular course, and though remaining mostly below the normal average, may sometimes considerably exceed it. This is shown by the following cases:—

Disease.	Number of Days Observed.	Minimum.	Medium.	Maximum.
MALES.				
Emphysema of lungs	0·6	1·3	2·3
Chronic Bronchorrhoea . . .	8	1·3	2·7	4·7
Cancer of the liver . . .	11	1·6	2·2	2·6
Subacute rheumatism of joints . . .	18	1·7	2·4	3·1
Hemiplegia, consequent on apoplexy . . .	35	1·0	2·7	5·2
Hydruria . . .	3	4·4	5·0	5·8
Dropsy, under influence of diuretics chlorides very much increased . . .	2	...	1·8	...
FEMALES.				
Diabetes insipidus . . .	14	3·2	4·8	7·8
Ascites . . .	15	1·7	3·0	4·7
Chronic rheumatism . . .	7	2·7	3·3	4·2
Spinal irritation	2·1	2·4	2·8
Amenorrhoea	2·1	2·2	2·3
Serophulosis	2·6	3·6	5·2
Tuberculosis of lungs . . .	10	1·6	...	3·9
Chronic erysipelas of face . . .	11	1·5	...	3·6

CHAPTER XXVII.

AMMONIA, NH_3 .

HISTORY AND OCCURRENCE.

AMMONIA became originally known as a product of destructive distillation of animal substances (spirit of hartshorn). It is practically obtained in the greatest masses as the product of the physiolytic of animal matters, particularly the urine, but great quantities also result from the processes for the manufacture of gas from coal. The chemolysis of all albuminous substances yields from three to four per cent. of the dry substances in the shape of ammonia. Ammonia is contained in air and water, and in the earth everywhere and all times.

According to Liebig, fresh healthy urine contains only very small or very doubtful traces of ammonia, and gives no precipitate with chloride of platinum. The crystals which form over night in urine mixed with chloride of platinum exhibit all the properties of the chloride of platinum and potassium. And if chloride of platinum and ammonium should be mixed with them, it is uncertain whether these are not due to the decomposing influence of the chloride of platinum upon the organic constituents of the urine. Lehmann and Scherer shared the doubts of Liebig regarding the presence of ammonia as a normal ingredient in urine. The analysis of Heintz, however, have proved that ammonia, if not always, is at least very frequently present in urine. The researches of Boussingault also seem to indicate the normal presence of ammonia in the urine.

The best proof as yet advanced of the regular presence in the urine of certain quantities of ammonia seems to be afforded by the analyses of Neubauer, who adopted the method of Schlösing for the volumetrical analysis of ammonia in the urine.

Some urinary deposits occurring in healthy urine contain urate of ammonium. The deposits are more common in the urine of disease, and there not always the products of alkaline decomposition.

Ammonia appears in large quantities in urine as soon as the urea has commenced to decompose. It then appears as carbonate, acetate, benzoate, phosphate, joining sodium on the one,

magnesium on the other hand, and as urate. While the former salts are dissolved the latter are deposited, the phosphate of magnesium and ammonium in the form of crystals, the urate of ammonium in dumb-bells and globular masses with spinous projections.

Ammonia further appears in every urine as soon as it is heated or subjected to distillation in a retort. The fluid which goes over will contain ammonia to the last—a phenomenon which has been explained by the decomposing influence of the acid phosphate of sodium upon urea. The phosphate of ammonium and sodium thus formed has the property of giving off its ammonia at a temperature of 100° , and the acid phosphate thus left is again and again a generator of ammonia, as long as any organic substances are left capable of yielding that base. During the whole period of distillation the urine in the retort retains a strongly acid reaction.

Physical and Chemical Properties.

A coercible gas, of a powerful pungent smell, strongly attached to water, and yet easily diffusible from this solution into the air, ammonia presents highly characteristic features. Volatile at all temperatures, and driven out of its combinations by fixed alkalis, again readily combining with acids, it is easily separated from the numerous ingredients of the urine, obtained pure, and its quantity determined.

In a mixture of perfectly neutral solutions of sulphate of silver and arsenious acid, the slightest trace of ammonia causes immediately a delicate but dense yellowish-white precipitate of arsenite of silver, which is easily soluble in the slightest excess of acid. This is the most delicate test for ammonia. Upon this I have based the following proceeding:—

Demonstration of the Presence of Ammonia in Urine.

The ammonia, which has been liberated from urine by means of milk of lime, is made to pass in the form of gas into a solution of sulphate of silver and arsenious acid; the precipitate ensuing is evidence of its presence.

The precipitate which phospho-molybdic acid gives in urine acidified with nitric acid (see chapter on Reducine) contains all the ammonia present in the urine employed. It can be obtained by distilling the precipitate with caustic baryta solution for a short time, and collecting the distillate in hydrochloric acid. In this solution the ammonia can be estimated by the platinum method.

Determination of the Quantity of Ammonia in Urine by Volumetrical Analysis.

The method just described may, with slight modifications, be used for determining the quantity of ammonia thus evolved.

Into a potash bulb is put a known amount of sulphuric acid of known strength, and the ammonia evolved from the urine by lime is made to pass through it by means of an aspirator. All ammonia of the urine will be combined with the sulphuric acid in the apparatus. The acid, thus combined with the ammonia, is now put into a beaker, and saturated with a solution of caustic soda of known strength. The point of neutrality is indicated by the appearance of a white precipitate of arsenite of silver, when the solution of sulphate of silver and arsenious acid has previously been added to the sulphuric acid, and by the reappearance of the blue colour when tincture of litmus has been used as the indicator. The former test is particularly useful when we have to work with artificial light, which does not permit the distinctions between red and blue litmus to be accurately perceived. From the amount of solution of soda used less than would have been required for saturating the same bulk of sulphuric acid of known strength, if no ammonia had been combined with it, the amount of ammonia is found by calculation.

The following method is based upon the fact that ammonia evaporates from its watery solution, and, if confined with free sulphuric acid in a closed space, is entirely absorbed by the acid. The rest is done by volumetrical analysis as above.

Preparation of Standard Solution of Sulphuric Acid.—Fourteen grm. of hydrated sulphuric acid are diluted with 200 grm. of water; and, after the mixture has cooled down to the ordinary temperature of the air, the amount of sulphuric acid contained in every 10.0 c.c. is determined by means of chloride of baryum in the usual way. If, for instance, we have found that 10 c.c. of the dilute acid contain 0.505 grm. of sulphuric acid, they will be exactly neutralised by 0.2146 grm. of ammonia, 1 c.c. of the dilute acid therefore corresponds to 0.02146 grm. of NH_3 .

Preparation of Standard Solution of Caustic Soda.—A dilute solution of freshly prepared soda in alcohol is made, and its strength is determined by finding the quantity required to neutralise 10.0 c.c. of the sulphuric acid just described. To 10.0 c.c. of the sulphuric acid, therefore, reddened by tincture of litmus, or mixed with the solution of sulphate of silver and arsenious acid, the solution of soda is added from a burette until the point of neutrality is indicated by the restoration of the blue colour of litmus, or the appearance of the precipitate of arsenite of silver. Suppose we have used to this point 30.0 c.c. of the solution of soda, then we know that every cubic centimetre of it exactly corresponds to 0.00715 grm. of ammonia; as the 10.0 c.c. of sulphuric acid, which were neutralised by 30.0 c.c. of soda, correspond to 0.2146 grm. of NH_3 .

Application of the Fluids.—20.0 c.c. of fresh filtered urine are put into a glass or porcelain dish of four inches in diameter, and one

inch in height. A triangle, made of a glass rod, is now put across the top of this dish, to support a smaller flat dish containing 10.0 c.c. of the standard sulphuric acid. This is now placed under a receiver on a ground glass-plate, closed hermetically by the aid of tallow. A dinner-plate and some mercury may also be used for the purpose. When the entire apparatus is thus completed, 10.0 c.c. of milk of lime are added to the urine in the lower dish, and the apparatus is quickly closed and put aside. After the lapse of forty-eight hours the whole of the ammonia formerly contained in the urine will be found to have been driven out, and to have been absorbed by the sulphuric acid in the upper dish. If the sulphuric acid is now neutralised by the standard solution of soda, so much less of this solution is required as is equivalent to the amount of ammonia contained in the acid. Thus, if the 10 c.c. of sulphuric acid (containing 0.505 gm. of SO_4 , corresponding to 0.2146 gm. of NH_3), after exposure to the vapour of ammonia evolved from the urine under the glass shade, require only 26 c.c. of the solution of soda instead of the 30 c.c. for which they are graduated, they have absorbed an amount of ammonia equivalent to 4 c.c. of the solution of soda, of which it has been seen that every cubic centimetre corresponded to $\frac{0.2146}{30} = 0.00715$ gm. of NH_3 . The 20 c.c. of urine, therefore, evolved or contained $4 \times 0.00715 = 0.0286$ gm. of NH_3 . 1000 gm. of urine would therefore contain 1.43 gm. of NH_3 ; and every other quantity in proportion.

Healthy fresh urine, free from mucus, does not undergo alkaline decomposition during the first forty-eight hours after being passed. But it is not so with the urine from patients, which very frequently begins to decompose a few hours after emission. Such urine, therefore, requires some precautions; the colouring and other easily decomposing matters may be removed by means of a mixture of equal volumes of solutions of basic and of neutral acetate of lead. Of this mixture 30 c.c. are mixed with an equal volume of urine, and of the liquid filtered from the precipitate 40 c.c., corresponding to 20 c.c. of urine, are taken for the analysis of ammonia. If the operator will take a little more trouble, he may control the analysis performed *with* milk of lime, by putting urine into a second apparatus *without* it. If the latter evolve no ammonia, spontaneous decomposition of the urine has probably not taken place.

The method of finding the amount of ammonia in urine by means of chloride of platinum, given by Heintz, requires much time for its execution. The amount of ammonia found by Heintz in the urine of twenty-four hours was more than double the quantity of that found by the above analysis of Neubauer, a fact which adds to the probability that

chloride of platinum produces ammonia in urine by decomposition of some of its constituents, not being simple salts of ammonia. Tidy and Woodman ("Proc. Royal Soc." 20 (1872), 362) estimated ammonia in urine, diluted until all colour had disappeared, by the Nessler test, comparing the tint with the tint of a solution of ammonia of known strength, according to the mode applied in water analysis.

Quantity of Ammonia Discharged in the Urine during Twenty-Four Hours by Healthy Individuals.

Neubauer examined the urine of two male individuals of twenty and thirty-six years of age respectively. The average of twelve analyses of the urine of the man of twenty years gave 0.6137 grm. of ammonia for twenty-four hours. The average of the second subject, as found by the same number of analyses, was much higher than that of the first, namely, 0.8351 grm. of ammonia for twenty-four hours. The minimum was 0.3125; the maximum 1.2096 grm. of ammonia each day. Expressing these facts in round figures, we may say that the average amount of ammonia excreted by a healthy man is, minimum, 0.3; average, 0.7; maximum, 1.0 grm.

Physiological Origin of Ammonia.

The only reliable knowledge on this point consists in the following facts:—*The ammonia of the salts of ammonia, when the latter are taken into the stomach, passes unchanged through the system and is discharged in the urine* (Neubauer). The subject of his experiments was the young man of twenty years of age, whose average discharge of ammonia during one of twelve days had been ascertained to be 0.6137 grm. He took now 2 grm. of chloride of ammonium in a glass of water for five successive nights; and in the urine collected for five successive periods of twenty-four hours, analysis showed an excess of 9.957 grm. of chloride of ammonium over the amount of ammonia previously ascertained to be the normal average.

It remains to be seen whether caustic ammonia and carbonate of ammonia are eliminated in a similar manner. It remains also to be ascertained whether the organism produces any ammonia under ordinary circumstances, or whether the ammonia in the urine is simply introduced by our food and drink, or by the air which we breathe. Some articles of food are rich in ammonia, *e.g.*, young vegetables. The smoke of tobacco contains a large share of ammonia; and any person remaining for any length of time in a room filled with it must inhale such quantities of ammonia as must materially increase the ordinary amount in his urine.

Pathological Indications.

If what some have ventured to bring forward as a defined feature of certain forms of disease of the kidneys can really be shown to exist, namely, that the urea retained in the blood may there undergo decomposition into carbonate of ammonium, and give rise to the symptoms described as uræmia, the pathological indications of ammonia in the urine would be all-important in those diseases. And though quantities of ammonia might be excreted by the lungs, skin, and bowels, yet the urine would be that excretion in which the ammonia would be most accessible to our analysis. However probable such a process, under given circumstances, may be, actual and direct proof would be required; and this we cannot say to have been afforded by the originators of the theory. We know, on the contrary, that the test said to be diagnostic of the presence of ammonia in the breath, the formation of white vapours on contact of the breath with a glass rod dipped in hydrochloric acid, frequently fails in cases with the most marked symptoms of uræmia. This would only show that the ammonia is not exhaled in some cases, but not that it is not present in the blood causing the uræmia. Anyhow, we must expect further proofs, analyses of the blood and the excretions, before we can give that importance to toxæmia, as a cause of various severe affections, which by various authors has been attributed to it. It is the same with putrid or septic fevers, under those conditions in which the blood is said to be in a state of dissolution. For all we know, ammonia may be a product of these pathological processes; and then we might expect to find it, in part at least, in the urine.

Tidy and Woodman found the ammonia diminish to about half the normal quantity (from 0.162 grm. in twenty-four hours to 0.081) in acute rheumatic fever, albuminuria, phthisis, and nervous diseases; in erysipelas, small-pox, typhus and typhoid fever it fell to one quarter (0.0405). Normal quantities were met with in cancer, heart diseases, chronic alcoholism, and chorea; an increased amount was observed in gout and diabetes. In moribund conditions it disappears from the urine almost entirely.

CHAPTER XXVIII.

TRIMETHYLAMINE, C_3H_9N .

HISTORY AND LITERATURE.

THIS is one of the substituted ammonias, and was discovered by A. W. Hofmann ("Ann. Chem." 78 (1851), 253; 79 (1851), 11). Its presence in urine was first shown by Dessaignes ("Ann. Chem." 100 (1856), 218); "Compt. Rend." 43, 670).

Occurrence.

It is found in living plants, such as the leaves of *Chenopodium vulvaria*, and the flowers of *Cratægus oxyacantha*. Like ammonia, it is a product of the destruction by putrefaction, pyrodistillation, or chemolysis of many animal substances. It is formed in particularly large quantities under influence of the processes just named from brain, nerve, and yolk matter, from the male and female roe of fish, and from bile, owing to the presence in them of choline or neurine in an organically combined state. This choline is trimethyl-oxethyl-ammonium oxyde or hydrate, and, under the decomposing influences just mentioned, easily yields trimethylamine and other products not yet isolated. This explains its presence in the brine from pickled herrings (Hofmann, "Ann. Chem." 83 (1852), 116). It is made synthetically, by gradually substituting in ammonia one atom of hydrogen after the other by methyle, and by other methods.

Chemical Characters.

Trimethylamine is a volatile base, which smells like ammonia and like sea-fish at the same time. It combines with acids, and yields crystallised salts. It is not more poisonous than, and in small doses acts upon animals like, ammonia. Its structure may be represented by the formula N,CH_3,CH_3,CH_3 .

Mode of Obtaining from Urine.

When large quantities of human urine are distilled, a distillate is obtained, having a strong smell of ammonia, and also of sea-

fish. When a little over-saturated with hydrochloric acid, it assumes a reddish colour. By crystallisation a large amount of chloride of ammonium is separated; the mother-liquor is evaporated to dryness, the residue extracted with alcohol, and the alcoholic solution is mixed with tetrachloride of platinum. After several crystallisations, fine crystals of the double salt of trimethylamine and tetrachloride of platinum are obtained, containing 37.17 Pt., and 40.22 Cl, and having the formula $C_3H_9N_2Cl_4Pt$.

Sixty-five litres of fluid, being previously condensed urine, gave 2200 grm. of chloride of ammonium, and only 17 grm. of the platinic chloride salt of trimethylamine, corresponding to only 3.7 grm. of free trimethylamine.

CHAPTER XXIX.

POTASSIUM AND SODIUM.

HISTORY AND OCCURRENCE.

THE carbonates of these metals, and the chloride of sodium have been known from time immemorial. But while the use of common salt as an ingredient of food has been a necessity to mankind for thousands of years, the very existence of potassium in the food and bodies and excretions of animals was unknown up to recent times. Potash was believed to be a product of the life of the plants, from the ashes of which it was extracted, until Klaproth, in one of the most luciferous essays, showed that it also occurred in minerals. From that time chemical analysis traced these metals more closely through the tissues and juices of plants and animals, and they were found to possess each a special function in vital processes, and could not replace each other. It was ascertained by Liebig that the salts of potassium predominated in the muscles to the almost entire exclusion of sodium salts, whereas they occurred only in very small quantities in the blood, in which, however, sodium salts prevailed. In the bile of the higher vertebrates the specific organic acids were found in combination mainly with sodium, while in certain fishes potassium formed the electro-positive ingredient of bile. The investigation of the distribution of these metals in the various parts of plants led to a consideration of their relations in food, and the conclusion became obvious that the presence of potassium salts was an important item in the total of its value, and that their absence diminished the value of any food almost as much as it decreased the fertility of any given soil.

Chemical Properties of Potassium Salts.

The atomic weight of potassium, K, is 39. Its presence in small quantities is most easily ascertained by spectrum analysis. All potassium salts on being heated on a platinum wire in the flame of a Bunsen's burner give a spectrum showing a red line in the least refracted part of the spectrum, a slight continuous illumination in yellow, green, and blue, and a violet line in the most refracted part of the spectrum. Spectrum analysis

therefore enables us to ascertain the presence of potassium in mixtures in which sodium prevails. The violet and red light of potassium vapour is very evident when its pure salts are heated in the colourless gas flame, or dissolved in burning spirit, but the presence of sodium entirely hides them from the eye under these circumstances. This effect of sodium can be eliminated by looking at the flame through a dark blue glass, or a vessel filled with a solution of indigo or prussian blue, when, if potassium be present, the flame presents the violet appearance. When larger quantities of potassium salts are present they may be recognised by the combination which they yield with platinum-tetrachloride, namely, the orange-yellow crystalline precipitate of the composition $2(\text{KCl})\text{PtCl}_4$. This is somewhat soluble in water, but insoluble in alcohol; and whenever it is intended to determine potassium quantitatively by this test, its solution mixed with platinum-tetrachloride and some hydrochloric acid is evaporated to near dryness, and then treated with alcohol, which leaves the potassium compound undissolved. The potassium salts further yield a characteristic crystalline precipitate either immediately or after some time when they are mixed with tartaric acid until the mixture is strongly acid, and well shaken. This compound is monopotassic tartrate, formerly termed acid tartrate, or ditartrate of potassium, $\text{C}_4\text{H}_5\text{KO}_6$; it is soluble in 180 parts of cold water, but dissolves easily in mineral acids and alkaline fluids.

Chemical Properties of Sodium Salts.

Atomic weight of $\text{Na}=23$. Sodium salts impart an intensely yellow colour to Bunsen's flame or burning spirit; in the spectrum they produce a yellow line in the position of the line D of Fraunhofer's solar spectrum; and this D line of the sun is itself due to the reversion of the spectrum of sodium, that is to say, to an absorption of yellow rays, emitted from the sun's solid glowing nucleus, by the less hot but still incandescent gaseous envelope of the sun, of which sodium is a principal ingredient. Sodium forms but few insoluble combinations, and cannot be quantitatively determined by transformation into any such compound. It is always determined as a residue in combination with sulphuric acid.

Mode of Obtaining the Alkalies from Urine.

They may be obtained in a pure state by the process to be related in the next paragraph, which serves for their quantitative determination. But they may also be separated first as chlorides, phosphates, and sulphates, by evaporation of the urine and crystallisation, and then separated from their relative acids, or diagnosed in these combinations themselves. When it is intended to separate the urinary salts by fractional crystallisation, large quantities should be treated.

Mode of Determining the Quantity of Potassium and Sodium in the Urine.

The rationale of the analysis is to remove sulphuric and phosphoric acid and organic matters, to transform the alkalies entirely into chlorides, and then to separate them by making one of them insoluble.

Of a solution of one part of acetate of baryum in 20 parts of water, made strongly alkaline by means of ammonia, one volume, say 20 c.c., is mixed with two volumes, 40 c.c., of urine. After the precipitate has begun to settle, it is separated from the fluid by filtration. Of the alkaline filtrate, which contains an excess of baryta, 45 c.c., corresponding to 30 c.c. of urine, are evaporated on the water-bath in a platinum dish, dried, and exposed to red heat until the carbon is entirely burned. Water is now added to the ashes until the soluble part is entirely dissolved. After the addition of some ammonia, carbonate of ammonium is added, to precipitate all baryum in the form of carbonate. The fluid is now separated from the insoluble parts and precipitate by filtration, and the filter is washed carefully. The filtered fluids are then acidulated by means of hydrochloric acid, evaporated in a platinum capsule of known weight, exposed to a gentle red heat, and weighed. The alkalies, the weight of which in the form of chlorides has thus been ascertained, are dissolved in a little water; chloride of platinum is then added in great excess, the mixture is evaporated nearly to dryness on the water-bath, and digested for several hours with spirit of 80 per cent. When the supernatant strata of the mixture indicate by a deep yellow colour that a sufficient amount of chloride of platinum is present, and when after frequent stirring of the mixture all chloride of sodium and platinum is probably dissolved, the solution is filtered from the chloride of potassium and platinum, and the precipitate and filter are well washed with spirit, dried, and weighed. The weight, less the weight of the filter, is chloride of potassium and platinum; 100 parts of the latter correspond to 30.51 parts of chloride of potassium. By subtracting the amount of the latter from the amount of the united chlorides, the rest gives the amount of chloride of sodium. The amount of chloride of potassium found, gives, by multiplication with 0.6317, the corresponding amount of potash; and the amount of chloride of sodium found, multiplied by 0.5302, gives the corresponding amount of soda.

Physiological Relations of Potash and Soda.

The facts adduced by Liebig are of so remarkable a nature, that to follow them out promises to be a source of progress in practical medicine. The analysis of the urine will always be the principal means for ascertaining the proportions of these alkalies

to each other, and to the other ingredients of the juices of the body. The problem is therefore a physiological one; and the analysis above detailed should not be considered as a mere exercise in the laboratory.

Many animals take with their food no phosphate of sodium, a salt indispensable to the integrity of the blood and body. But they take phosphate of potassium and chloride of sodium. In these animals, however, we find in the blood phosphate of sodium, and in the muscles chloride of potassium; neither of which salts they have taken with their food. From this fact, and from other experiments in the laboratory, the conclusion is inevitable, that phosphate of potassium, when mixed with chloride of sodium, gives a part of its potassium off to some chlorine, which in its turn parts with some sodium. The latter joins the phosphoric acid, phosphate of sodium being formed.

The relations of the salts of potassium to the muscles are not as yet understood. But the same physiological law which confines phosphate of sodium to the blood, and makes it indispensable there, is, no doubt, active in confining the salts of potassium to the muscles. To bring about an understanding of these relations is a problem of experimental physiology.

Distribution of Acids amongst the Alkaline Metals.

It is certainly very difficult to show in which manner the various acids and bases contained in the urine neutralise each other, or are decomposed by each other. But we may obtain some insight into these relations by the usual process of determining the total quantities of all acids on the one, and the total quantities of all bases on the other side, and then allowing them to be neutralised by each other in the order of their supposed affinity. Another means for attaining the same object consists in evaporating the urine, and ascertaining the manner and order in which the various combinations crystallise. By this latter method we obtain the following individual salts of the alkali metals:—

Sodium Chloride, NaCl, At. W. = 58.5.

It crystallises in little cubes from evaporated urine; they are frequently so arranged as to form pyramids, and under certain conditions these pyramids pass into regular octahedra. The cubes of sodium chloride do not fuse when heated on platinum, whereas the cubes of potassium chloride fuse easily under these conditions. When water is digested with sodium chloride at the ordinary temperature of the air during 24 hours it is found to contain 31.84 grm. of the chloride in every 100 c.c., and this occurs so invariably that a saturated solution of sodium chloride may be made the standard and starting-point of important

analytical processes, as we have shown in the chapter on the analysis of urea.

Potassium Chloride, KCl , At. W. = 74.5.

This salt crystallises in cubes, which are fusible on platinum, and thereby easily distinguished from the sodium cubes. It has less tendency to form the octahedral crystals than the sodium salt. It is more hygroscopic than the sodium salt. The solution when not too dilute gives the orange precipitate with platinum tetrachloride already described. The watery solutions of crystals of the potassium and sodium chloride each give the reactions for chlorine, namely, a white precipitate with silver nitrate insoluble in nitric acid, soluble in excess of ammonia; a white precipitate with the nitrate of mercury suboxide, which is insoluble in acids, blackened by ammonia; their concentrated solutions, when mixed with nitrate of mercury-oxide, deposit a mass of white crystals of mercury dichloride; but dilute solutions of these reagents effect no visible change, although the double decomposition continues until the whole of the alkali metal has become nitrate, and the whole of the mercury dichloride. This reaction we have described above as the basis of a particular method for determining chlorine in urine. From an acid solution of the chlorides the entire amount of chlorine can be removed by silver, and determined by weighing the silver chloride. From a neutral solution of the chlorides all chlorine may be precipitated if a solution of silver nitrate is added until neutral potassium chromate produces reddish precipitate of silver chromate. This reaction is the basis of a volumetric determination of chlorine in urine.

Sodium and Potassium Sulphate.

These salts crystallise from the mother-liquor of the urinary crystals, particularly by the influence of cold. But they can also be precipitated by alcohol, in which they are almost insoluble, while the chlorides are very soluble, and the phosphates soluble to some extent in alcohol.

Sodium sulphate, $\text{Na}_2\text{SO}_4 + 10 \text{ aq.}$, At. W. = 332, crystallises as Glauber's salt, in glassy crystals, which wither in the air. On evaporation of a saturated solution, or by precipitation with alcohol, it is obtained in anhydrous rhombic octahedra.

Potassium sulphate, K_2SO_4 , At. W. = 174, on the other hand, crystallises without water in glassy, hard, small crystals, which, though anhydrous, decrepitate by heat.

The sulphates of potassium and sodium can be completely transformed into the chlorides by repeatedly subjecting them to the influence of red heat in the presence of ammonium chloride.

Sodium and Potassium Phosphates.

Sodium phosphate, HNa_2PO_4 , occurs in the urine and other animal fluids, and is obtained by crystallisation with 24 atoms of water of crystallisation. In that state it corresponds to the ordinary sodium phosphate of the pharmacopœas. It forms glassy oblique rhombic prisms, effloresces in the air, fuses at a gentle heat, and at 300° loses 60 per cent. of water; at a red heat it loses the molecule of basic water, 2.49 per cent., and becomes pyrophosphate, $\text{Na}_2\text{P}_2\text{O}_7$.

The *acid sodium phosphate*, NaH_2PO_4 , is formed in urine under the influence of the organic acids which are produced by the animal process. It crystallises from evaporated urine in different forms, of which the rhombic prism is the most common. The crystals contain 2 atoms of water, which they lose at 100° . At between 190° and 204° they lose one atom of basic water, and become monohydrated pyrophosphate; at 204° to 244° they are transformed into metaphosphate, NaPO_3 .

The *potassium salt*, K_2HPO_4 , corresponding to the ordinary sodium phosphate, cannot be obtained in the crystallised condition, and is, perhaps mainly for this reason, usually not enumerated amongst the ingredients of urine or animal fluids. The acid salt, KH_2PO_4 , crystallises without water of crystallisation, and its crystals remain glass-like up to 204° . It is easily soluble in water, insoluble in spirit, has a strongly acid taste, and reddens litmus strongly, but the redness disappears on drying of the paper.

CHAPTER XXX.

CALCIUM AND MAGNESIUM.

OCCURRENCE.

CALCIUM and magnesium occur in the urine in combination with phosphoric acid, as acid phosphates and as urates, hippurates and kryptophanates in solution. The phosphates of earth are met with as deposits in alkaline urine, and as concretions in urinary calculi, of which they most frequently constitute the crust, but sometimes also the entire substance. In the urine of herbivorous animals calcium and magnesium frequently occur as carbonates.

Physical and Chemical Properties.

(a.) *Of Calcium Phosphate, $\text{Ca}_3\text{P}_2\text{O}_8$.*—This, the tribasic salt, is obtained by dissolving bone-ash in hydrochloric acid, and precipitating by ammonia. The addition of ammonia to urine also produces this precipitate, together with ammonio-phosphate of magnesium. Voluminous gelatinous flakes, which, on drying, shrink to a white amorphous mass. It is easily soluble in nitric and hydrochloric acid; when freshly precipitated, also in acetic acid. When this solution is allowed to stand some time, the phosphate has a great inclination to fall down in a crystalline state, particularly when the mixture is warmed a little, and the phosphate is prevalent. Freshly precipitated, it also dissolves largely in concentrated caustic potash. When dissolved in acids or in the urine, the phosphate contains only one atom of calcium, two atoms being withdrawn by the dissolving acid.

(b.) *Of Magnesium Phosphate.*—The addition of caustic potash to a solution in acid of magnesium phosphate produces the tribasic salt, $\text{M}_3\text{P}_2\text{O}_8$, which at 100° retains five molecules of water. But when ammonia is added to a solution of magnesium phosphate, then crystals of phosphate of magnesium and ammonium are precipitated, $\text{Mg}_2(\text{NH}_4)_2\text{P}_2\text{O}_8 + 12\text{H}_2\text{O}$, or $\text{Mg}(\text{NH}_4)\text{PO}_4 + 6\text{H}_2\text{O}$. This salt is easily soluble in acids, even acetic, insoluble in water containing excess of ammonia. It occurs in ammoniacal urine as a deposit, is found in the urinary passages in certain diseases, and encrusts certain urinary calculi. It is the principal constituent of the intestinal calculi of horses. It is

supposed that while calcium phosphate is dissolved in urine as acid salt, $\text{CaH}_2\text{P}_2\text{O}_7$, the magnesium phosphate is dissolved as half basic, $\text{Mg}_2\text{H}_2\text{P}_2\text{O}_7$, or MgHPO_4 . Its nearly neutral solution becomes turbid by boiling, but clears up again on cooling.

Separation of Phosphate of Calcium and Magnesium from Urine, and Determination of their Collective Amount.

This is effected by adding to urine some ammonia, until a strong alkaline reaction is observed. The earthy phosphates thus precipitated may be collected on a filter, washed, exposed to read heat and weighed. This residue contains on an average 67 per cent. magnesium pyrophosphate, and 33 per cent. tribasic calcium phosphate. Or, after collection on the filter, they may be redissolved in acetic acid, and in this solution the amount of phosphoric acid, found by the analysis described above, may, by the known atomic weights, indicate the amount of earths in combination. Or, if the phosphates of the alkalis are to be determined also, the analysis described in a previous chapter may be used, by which, in the first instance, the entire amount of phosphoric acid contained in the urine, and then of phosphoric acid in combination with the alkalis, is determined, the difference corresponding to the amount of phosphoric acid in combination with the earths.

Modes of Ascertaining the Separate Quantities of Calcium and Magnesium in Urine.

All the following methods are preceded by the separation from urine of both earths by means of ammonia, and by the solution of the washed precipitate in acetic acid. From the latter solution the calcium is always obtained as the oxalate. From this point the analyses begin to vary.

Determination of the Calcium as Sulphate.

The oxalate of calcium obtained by addition of oxalate of ammonium to the solution in acetic acid of the precipitate, which a measured quantity of urine yielded after addition of ammonia, is exposed to a strong red heat in a platinum capsule. To the lime thus transformed into carbonate, partly into caustic lime, some sulphuric acid is added, with great care, in small portions, by means of an elastic pipette, until an acid reaction is observed. After drying, and a second exposure to red heat, the calcium is obtained in the form of sulphate, which, by multiplication with 0.4118, gives the amount of lime contained in the sulphate.

Determination of the Magnesium as Pyrophosphate.

The filtered fluid obtained from the oxalate of lime in the course of the foregoing analysis, is treated with ammonia until alkaline, whereby the magnesium is precipitated in the form of $\text{Mg}(\text{NH}_4)\text{PO}_4 + 6\text{aq.}$, the so-called triple phosphate, or ammonio-phosphate of magnesium. As the crystals settle easily to the bottom of the vessel, this salt may be washed by decantation of repeated quantities of water, containing some ammonia added to it. It is then collected in the platinum capsule, and exposed to red heat. If collected on a filter, the latter, after removal of the greater bulk of the crystals into the platinum capsule, has to be burned separately by Bunsen's process. Precipitate and filter, when united, are then exposed to red and white heat. The triple phosphate, by losing all its water and ammonia, is thus transformed into pyrophosphate of magnesium of the composition $\text{Mg}_2\text{P}_2\text{O}_7$.

Hempel's Method of Determining the Calcium as Oxalate, by means of Permanganate of Potassium.

From the solution of the mixed earths in acetic acid the calcium is precipitated by oxalate of ammonium, collected on a filter, and, after washing, is dissolved in a few drops of hydrochloric acid. To this solution, after warming it a little, a graduated solution of permanganate of potassium is added, so long as discoloration continues to take place. From the amount of solution of permanganate of potassium used, the amount of oxalic acid is found, and from this the amount of calcium originally combined with phosphoric acid.

Preparation of the Solution of Permanganate of Potassium.

As the solution of permanganate cannot be kept for any length of time without undergoing changes, its graduation has to be checked before each analysis. For this purpose, and for the original graduation, a solution of oxalic acid in water is used, which in every cubic centimetre contains 10 milligrm. of oxalic acid. The solution of permanganate of potassium is then graduated so that 1.0 c.c. will exactly suffice to oxydise 10 milligrm. of oxalic acid, and to make the signal of the completed oxydation by the appearance of the red colour.

The solution of oxalic acid is made by dissolving 1 grm. of the acid, dried at 100° , in 100 c.c. of water. Of this solution 10 c.c. are taken by means of a pipette, and transferred to a beaker. We now add, from a burette, of the solution of permanganate which is to be graduated, as much as necessary to produce the lasting red test. Supposing that 8.3 c.c. have been used for that purpose, we then add to every 830 c.c. of the solution 170 c.c. of

water, whereby we obtain 1000 c.c. of solution, of which 10 c.c. will exactly suffice for oxydising 10 c.c. of the solution of oxalic acid, containing 100 milligrm. of the acid.

It is, however, less troublesome to merely determine the quantity of solution of permanganate of potassium required for oxydising a known amount of oxalic acid, without adjusting its bulk to that of the solution of the acid.

If, therefore, the above solution be taken as it is, without adding the 170 c.c. of water, then its value would be expressed by $8.3 \text{ c.c.} = 100 \text{ milligrm. of oxalic acid}$. The calculation after the use for real experiment would therefore be $8.3 \text{ c.c. of standard solution} : 100 \text{ milligrm. of oxalic acid} = x \text{ c.c. standard solution} : x \text{ milligrm. of oxalic acid}$.

This analysis has been combined by Vogel with the volumetrical analysis of phosphoric acid, so that by two analyses the quantities of phosphoric acid and both earths are determined. He for that purpose takes the precipitates from two equal quantities of urine, and determines in the one the entire amount of phosphoric acid, in the other the amount of calcium as just described. From the total amount of phosphoric acid the equivalent for calcium is now deducted; the rest of the acid indicates the amount of magnesium with which it was combined.

The operator must take care to use a Gay-Lussac's burette for the solution of permanganate of potassium, as this fluid is decomposed by the cautchouc of Mohr's burette.

Deposits of Earthy Phosphates.

As a rule, deposits of amorphous earthy phosphates with three atoms of base can exist only in urine exerting an alkaline reaction upon test-paper. The presentation of an acid reaction by urine, therefore, excludes the possibility of the occurrence of these deposits. There is only one (questionable) case in which a deposit of an earthy phosphate is compatible with an acid reaction of the urine, namely, when urine containing little or no free acid exerts an acid reaction from the presence of chloride of ammonium. In this case a deposit of phosphate of magnesium may perhaps exist; for this salt is little or not soluble in chloride of ammonium. But phosphate of calcium is so soluble in the latter salt, that it could not exist as a deposit so long as any acidity of the chloride of ammonium is not neutralised.

The observations which are said to have been made of urine having an acid reaction, and yet containing a permanent deposit of phosphates, if they cannot be explained in the way just detailed, must be considered as fallacious. I have made some observations, which may serve to explain the manner in which such statements have arisen. Clear acid urine was allowed to stand for three hours, when a pellicle of phosphates was observed

on the surface. Blue test-paper, immersed an inch deep into the fluid, on being withdrawn had become red. Another piece of the blue test-paper was now laid flat upon the surface of the fluid, when no reaction took place. The upper stratum of the urine had evidently become alkaline under the influence of the air, while the lower strata had retained their acidity.

Urine may be acid for a short time and yet contain a deposit of phosphates; or it may contain a deposit of phosphates for a short time, and yet remain acid, under the following circumstances:—If to acid urine in the bladder a secretion of alkaline urine be superadded, and the person remain very quiet, the lower strata of the urine in the bladder may be alkaline, and contain a deposit, while the upper remain acid. Of course this may vary according to the different densities of the two secretions. My explanation is based upon a case in which urine was discharged acid, and yet thick from the presence of phosphates. But the upper strata of the urine soon became quite clear, and a little cloud at the bottom of the vessel dissolved on agitation.

We have already seen that an alkaline reaction of the urine may be due to various causes, and have distinguished between alkaline reaction from fixed alkalies, derived from the blood, and that which is due to the presence of ammonia from decomposition of urea. The deposits of earths taking place under the neutralising influence of both alkalies are identical as regards phosphate of lime, different as regards phosphate of magnesia. For the latter is deposited by fixed alkali, as $Mg_3P_2O_8 + 5 aq.$, while in the presence of ammonia it takes up one molecule of this base and water of crystallisation, and appears as $Mg(NH_4)PO_4 + 6 aq.$ A deposit containing this latter salt is therefore due to the presence of ammonia from decomposed urea. If the acid, by means of which phosphate of calcium is kept in solution in the urine, be a volatile one, namely, carbonic acid, as was observed in one case, which will be quoted in another page, the spontaneous or intentional evaporation of the acid may cause a deposit of lime to appear.

Deposits of Phosphate of Lime.

Physical Characters.—Deposits of phosphate of calcium, as usually occurring in the urine and mixed with magnesium, are always white, amorphous, under the microscope appearing in granules, sometimes of a greenish tinge, which exert a refracting action upon light. Crystallised deposits of this substance have also been observed to constitute or be an admixture of some crystalline sediments.

They have also been produced artificially in urine.

Crystallisation.—Phosphate of calcium may be obtained in a

crystalline state from its solution in acetic acid. When this solution is allowed to stand some time, the phosphate has a great inclination to fall down from it in a crystalline state, particularly when the mixture is warmed a little, and when the phosphate is prevalent. By precipitation of phosphate of sodium with chloride of calcium, an amorphous gelatinous deposit of phosphate of calcium is obtained. This after standing some days becomes transparent, like solution of gum. When a sunbeam is now allowed to fall on the precipitate, myriads of glistening crystalline points may be observed disseminated through the amorphous part of the deposit. Under the microscope these crystals appear as delicate, thin, clino-rhombic plates, very much like the crystals of oxalate of urea.

Chemical Diagnosis of Deposits of Phosphate of Calcium.—The common occurrence in neutral or alkaline urine is the first point to be observed. The deposit is insoluble in water, soluble in weak acids, such as acetic acid, and is again precipitated from the acid solution in its original form by ammonia. From the acetic acid solution oxalate of ammonium throws down oxalate of calcium. This latter test distinguishes it from the phosphate of magnesium, with which it is always mixed. Phosphate of calcium alone does not easily fuse before the flame of the blow-pipe.

When diffused in urine, the deposit appears like a dense cloud of mucous, from which it is not easily distinguished, because it is mostly mixed with it, and resembles it in colour. When it appears in urine on the application of heat, its resolution on cooling, or by the addition of an acid, distinguishes it from albumen.

Deposits of Ammonio-Phosphate of Magnesium.

Physical Characters.—Deposits of this substance always occur in well-defined crystals in ammoniacal urine. No substance commonly occurring in the urine, and being insoluble in water, presents the same glistening glass-like appearance.

Form of Crystallisation.—The triple phosphate crystallises in the rhombic system. The form most commonly met with is the vertical prism, combined with terminal planes derived from macro- and brachy-diagonal horizontal prisms. Some of these forms resemble hippuric acid very much. But there is this crystallographical distinction between them, that on crystals of hippuric acid we frequently observe planes derived from the rhombic octahedron, which in triple phosphate are scarcely ever met with.

Not rarely these crystals have a tendency to cross each other at regular angles. This is best seen in crystals obtained from blood. The latter serve to explain other forms observed in the

urine, namely, the stellæ, which are not merely acicular prisms cohering at one end, but prisms crossed at regular and symmetrical intervals. They very much resemble crystals of snow. These latter, however, being prisms of the hexagonal or rhombohedral system, cross at equal angles (of one sixth of the circle each), while the triple phosphate crystals cross at angles of which only four are equal, the other two being equal to each other.

The stellar and foliaceous crystals are not all formed by crossing only, some being appositions of groups of crystals in the prolongations of the axes of a central crystal. In this way the most fanciful forms are obtained.

The crystals of triple phosphate polarise light, and then appear tinted with prismatic colours. When seen in a sunbeam reflected through the polarising microscope, they appear fine objects for studying the phenomena of polarisation.

Chemical Properties.—When kept in water the triple phosphate disintegrates, the surface of the crystals becomes corroded, and at last there is nothing left but amorphous phosphate of magnesium. This corrosion is prevented by the presence of free ammonia, which makes them quite insoluble in water, and is therefore eligible as a preserving fluid for microscopical specimens. When the transparent crystals are exposed to a boiling heat, they lose water of crystallisation and become opaque. They are easily soluble in acetic acid, and from this solution may be obtained again by excess of ammonia.

When heated with a solution of potash, the triple phosphate is decomposed, the potash combining with the phosphoric acid and setting free the ammonia and the magnesia. The former volatilises, and may be detected by the smell, while the magnesia is precipitated.

Earthy Phosphates in Calculi.

Not quite 10 per cent. of all calculi have a nucleus of mixed phosphates. But these substances enter into the composition of about 34 per cent. of all calculi, forming either their body, one or more layers, or the crust. This shows that the presence of deposits of mixed phosphates in the urine does give rise to the formation of calculus, but that the presence in the bladder of other calculi more frequently causes a deposit of phosphates to be formed around them, in which respect every calculus is nothing else than a foreign body.

Prout found the proportion of phosphate of calcium calculi to the whole number contained in various museums as 1 to 117. The proportion of calculi composed of pure triple phosphate was 1 to 126. The relative proportion of the mixed phosphates he put as 1 to 12. The general proportion of all the calculi,

arranged under the heads of the phosphates in different museums, he found as 1 to 10. In alternating calculi, the phosphates succeeded to uric acid in the proportion of 1 to 9. The ratio in which the phosphates succeeded to urate of ammonium (and sodium) was as 1 to 12; and in which the phosphates succeeded to the oxalate of calcium was as 1 to 7. On the contrary, three instances only occurred in which the uric acid, or urate of ammonium, succeeded to a phosphate; and the proportion in which the oxalate of calcium succeeded to the phosphates was as 1 to 253 only. The general proportion in which the phosphates succeeded to the other ingredients was as 1 to 4.

From these facts, Prout deduced the general law that in urinary calculi a decided deposition of the mixed phosphates is not followed by other depositions.

Calculi of phosphate of calcium have mostly a smooth surface, and are composed of concentric layers, which, when the calculus is broken, separate from each other with great facility, forming detached crusts. These are almost infusible before the blowpipe, requiring for fusion so intense and prolonged a heat, that few can succeed in fusing them (Bowman). The chemical characters of these calculi are those of phosphate of calcium, as described above.

Calculi composed entirely of triple phosphate are generally crystalline, or consisting of aggregated prismatic crystals; they often contain cavities filled with large and perfect crystals of triple phosphate, or have their surface covered with a smaller variety of them. Specimens of this kind are contained in the Museum of the College of Surgeons.

Before the blowpipe, the triple phosphate gives off the smell of ammonia, swells up, gradually becomes grey, and ultimately fuses.

Calculi composed of phosphate of calcium and triple phosphate are commonly called fusible calculi, from the readiness with which they fuse before the blowpipe, giving off ammonia and water, and leaving a mixture of phosphate of calcium and pyrophosphate of magnesium.

Calculi of Phosphates of Earths arising in the Urinary Bladder in Typhus.

The relaxation of the striated muscles which takes place in typhus fever frequently causes, particularly in old persons, great distention of the urinary bladder. This distention is not rarely overlooked, as there is no impediment to the flow of urine by abdominal pressure. It is also accompanied with involuntary passing of the urine, particularly in young persons. In children I have seen it pass into retention, with deposits forming in the bladder. It is most frequent amongst men in the later periods

of life. The retention does not, so long as the urine has the acid concentrated character of the febrile stage, produce any phosphatic deposits; but during the anæmic state of recovery ammoniacal decomposition takes place, mucus is secreted, phosphates are deposited, and calculi are formed, which increase rapidly, and if not removed by operation cause kidney disease and death. The calculi under consideration, four in number, came from such a case. They had the size of walnuts, were white, hard, and contained each a cavity of the size of a pea in their interior. The cavities were empty when observed, which was after the calculi had been dry for some time. There is little doubt that the contents of these cavities were originally mucus, upon which the outer matter had been deposited. The mucus drying up left the cavities.

Analysis of one of the Calculi.—The finely-powdered stone was almost entirely soluble in dilute hydrochloric acid, the solution being only slightly opalescent. The filtered solution gave on addition of ammonia a precipitate easily soluble in dilute acetic acid. On addition of oxalate of ammonium a minute precipitate of oxalate of calcium was observed. On adding caustic potash to the powdered stone ammonia was evolved. The calculus therefore consisted mainly of phosphate of magnesium and ammonium, with traces of phosphate of calcium and ammonia. There was no uric acid and no oxalate of calcium.

The quantitative analysis yielded some curious results. 1.0195 grammes during drying in the water-bath at 100 lost 0.4120 grammes, or 40.41 per cent. From the residue there were obtained by oxalate of ammonium, &c., 0.03 grammes calcium carbonate, corresponding to 0.031 grammes of phosphate of calcium ($\text{Ca}_3\text{P}_2\text{O}_8$), or 3.04 per cent. Further, 0.4482 grammes of pyrophosphate of magnesium ($\text{Mg}_2\text{P}_2\text{O}_7$), corresponding to 0.9892 ammonio phosphate ($\text{MgNH}_4\text{PO}_4 \cdot 6(\text{H}_2\text{O})$), or 97.02 per cent. of the original calculus.

$\text{Ca}_3\text{P}_2\text{O}_8$	3.04
$\text{MgNH}_4\text{PO}_4 \cdot 6(\text{H}_2\text{O})$	97.02
	<hr/> 100.06

As the 1.0195 grammes of calculus lost 0.4120 in weight during drying, while, if the loss had been that of five-sixths of the water contained in the triple phosphate, it should have amounted to 0.3633 only, there was an excess of 0.0487 lost. The question now arose whether this was water or ammonia.

1.2259 grammes of calculus powder were heated in the water-stove. After having been in it for about half an hour the powder was taken out, and a glass rod moistened with hydrochloric acid was brought near to it. Thick vapours of chloride of

ammonium were immediately formed. A piece of blue litmus paper, reddened by vapours of hydrochloric acid, was turned blue again while being held over the powder. The powder therefore lost both water and ammonia during drying at 100° , and, as was ascertained by five weighings, the more the longer the drying was continued.

A quantity of pure phosphate of ammonium and magnesium was now prepared, and when air-dry was brought into the vacuum over sulphuric acid. It was kept there for six weeks, and during that time weighed eight times, at nearly equal intervals. Each time it was found to have lost five or six centigrammes in weight. It is therefore clear that the crystallised triple-phosphate, when brought air-dry or nearly so into a vacuum, loses, besides adherent moisture, either water of crystallisation, or ammonia, or both.

The calculus thus contained in 100 parts—

Water, and little ammonia given off at 100° ,	40.41
Water and ammonia given off by red heat,	12.59
Pyrophosphate of magnesium,	43.96
Phosphate of calcium,	3.04
	<hr/>
	100.00

Physiological Quantities of Earthy Phosphates in the Urine.

The proportion in which the phosphate of calcium in the urine stands to the phosphate of magnesium has been determined by Kletzinsky to be about two to one; namely, 67 parts of phosphate of calcium and 33 parts of phosphate of magnesium in 100 parts of mixed earthy phosphates precipitated from healthy urine.

The average amount of phosphates of the alkaline earths discharged by a healthy man in twenty-four hours, has been determined by Beneke to be 1.2 grm. Under ordinary diet, Lehmann discharged 1.09 grm.; Becker, 1.48 grm. These observations give, as the average of mixed phosphates during twenty-four hours, 1.28 grm.

Mosler and Hegar determined the quantity of earthy phosphates by calculation from their phosphoric acid. The former made two series of observations upon himself, the first series comprising six days in April, the second four days in October. His results were as follows:—

*Observations of the Quantity of Phosphoric Acid Combined with
Earths in the Urine.*

	First Series Amount of P_2O_5 .		Second Series Amount of P_2O_5 .	
	During one hour.	During one day.	During one hour.	During one day.
Minimum . . .	Grm. 0·015	Grm. 0·370	Grm. 0·007	Grm. 0·170
Medium . . .	0·048	1·152	0·015	0·390
Maximum . . .	0·075	1·800	0·027	0·660

In other healthy individuals, Mosler found the average per hour of P_2O_5 to fluctuate between 0·015 and 0·019 grm. Hegar found from observations, extending over eight days, that he discharged 1·31 grm. of phosphoric acid in combination with earths. Six months afterwards the average of four days was only 0·902 grm. of P_2O_5 . Neubauer determined directly the amount of lime and magnesia discharged by two healthy persons. His results are arranged in the following table:—

*Observations of the Quantity of Lime and Magnesia Dis charged
during Twenty-Four Hours.*

	First Individual. Average of seventeen days.		Second Individual. Average of twenty-one days.	
	Lime.	Magnesia.	Lime.	Magnesia.
Minimum . .	Grm. 0·057	Grm. 0·096	Grm. 0·118	Grm. 0·084
Medium . .	0·096	0·173	0·250	0·219
Maximum . .	0·169	0·271	0·356	0·262

From all the observations taken together, it follows that the amount of earthy phosphates in the urine varies in different individuals, and in the same individuals at different times. A general average for any given weight of individual can therefore not be drawn at present. It can only be obtained by extended observations on the urine, taking into consideration the quantities of earths ingested with the food, and those discharged by way of the bowels.

The influence which different qualities of food have upon the quantity of earthy phosphates discharged by the urine is well illustrated in the experiment of Lehmann. As we have already stated, when eating mixed food, his average amount of earthy phosphates was 1·09 grm. But when he restricted himself to animal diet, the amount rose to 3·56 grm., being more than three times his ordinary average.

Pathological Indications.

1. *The presence of precipitates of earthy phosphates in the urine is indicative of the alkaline condition of that fluid.*
2. *If the precipitate of earthy phosphates is entirely amorphous, we may conclude that the alkali which caused it was not ammonia.*
3. *If, however, the precipitate contains crystals of triple phosphate, it indicates the presence of ammonia, arising most probably from decomposition of urea.*

An excess or deficiency of earthy phosphates in the urine can only be ascertained by quantitative chemical analysis. The mere presence in the urine of a deposit of this kind, or its appearance in the urine on heating, is by no means indicative of an excess, as is yet too commonly believed. The originators of the term phosphatic diathesis and phosphuria, and their followers, linked a series of the most varied disorders together under this term, which had nothing in common but one symptom, namely, alkaline urine. The following facts and considerations may perhaps serve to explain some opinions, which, by the weight of authority, are rather widely circulated, but nevertheless require a thorough reformation.

Animal diet has a tendency to increase the acidity of the urine; vegetable diet easily makes it alkaline. The dyspeptic, therefore, eating little or no meat, will easily cause his urine to be alkaline by eating a little fruit, for which he not unfrequently has a longing. But even if no fruit has been partaken of, and but little meat, the secretion may be alkaline; in the former case from the presence of carbonates, in the latter from that of alkaline phosphates from the blood, which the free acid has not been sufficient to transform into acid salts.

What want of appetite for animal food causes in the dyspeptic patient, want of animal food causes in poor, old people. The alkaline urine of the octogenarian dependent upon parochial relief, is the consequence of his not being able to afford meat once a week. Hence, in these cases, the acidity of the urine is restored by a proper allowance of meat.

The anæmic girl and the diabetic patient are instances of the same character. In the former the phosphates may be altogether absent for a day or two, so that the urine, being alkaline, will form no deposit. Meat diet will soon restore acidity and phosphates. In diabetic patients phosphate of calcium is sometimes altogether absent, and the alkaline urine deposits the triple phosphate only. Lehmann observed such a case. The glittering crystalline deposit of triple phosphate contained no trace of lime. We may here observe that the microscopical analysis is not sufficient to prove the absence of phosphate of

lime. For Vogel observes that deposits of the latter salt are often so transparent, and their outlines are so little defined, that when mixed with the triple phosphate they are easily overlooked, unless the observer takes particular care in illuminating his object. It is for this reason that we cannot take any notice of statements regarding the occurrence of deposits of the triple phosphate, unmixed with phosphate of lime, which are not sustained by exact chemical tests.

Urine becomes alkaline when retained in the bladder for any unusual length of time. This will not so much occur when absolute retention takes place, as when from any cause the bladder is never emptied entirely of its contents. This causes irritation of the mucous membrane, and an increased discharge of mucus, which, being retained also, is present in unusual quantity. Whether by means of the mucus, or on its own account, we do not pause to discuss—but urea is decomposed, making the urine ammoniacal. A small part of this ammoniacal urine is always retained, and induces quickly an analogous decomposition in the fresh arrivals from the ureters. The urine is then discharged alkaline, thick, and fetid. But when the bladder is thoroughly emptied and washed out by injection, an acid urine will immediately collect in it.

This is the physiological explanation of these cases, as proved by experience, reason, and experiment. Let the retention be due to paralysis of the bladder, from whatever cause—affecting of any part of the spine, from hemiplegia or paraplegia, or from difficult childbirth; let it be due to the presence of sacculi of the bladder, to calculi or foreign bodies, to enlarged prostate, to stricture of the urethra; or let the retention be caused by the perverse will of insanity, in which excretions are frequently held back, entirely or in part; or let partial retention occur in the coma of fever—it will always have the same effect, decomposition of urea and ammoniacal urine.

There are some rare and extraordinary cases, in which phosphate of lime is said to continue to be discharged in the urine for a long time without apparently doing much mischief. Such a case is recorded by G. Bird. The patient was an old man, an habitual dyspeptic, and had laboured under pyrosis from boyhood. He had during many years been in the habit of passing almost milky urine, which on repose deposited such an extraordinary quantity of phosphate of lime, that he brought to G. Bird, at one time, more than an ounce of the salt. He had during the last fifty years been under the treatment of half the hospital physicians and surgeons in London. At the same time this man's general health was so good that there was scarcely an excuse for submitting him to any course of treatment, beyond the apprehension of the possible formation of a calculus.

Prout examined the body of a gentleman who during the greater part of his life had suffered from renal disease, remarkable for being attended by the secretion of large quantities of the earthy phosphates. Both kidneys were not only extensively disorganised, but most of the natural cavities, as well as many cysts, were found distended with numerous earthy concretions, of various sizes and composition. The concretions found in those cavities *to which the urine had access*, consisted of the phosphate and carbonate of calcium, and more or less of the triple phosphate of ammonium and magnesium, while those cavities or cysts distinct from the renal structure, and to which, therefore, *the urine had no access*, consisted of the calcareous phosphate and carbonate only, without any admixture of the triple phosphate.

From a consideration of many cases of earthy calculi it is apparent that the mere presence in the bladder of deposits of the earthy phosphates never gives rise to calculi. For such a concretion to form, it requires the presence of some binding material, such as ropy mucus, or a clot of blood, or fibrine. It is for this reason that urine, which deposits the earths in the bladder under the influence of fixed alkali, has never been known to form a calculus. It is only with the aid of hæmaturia, or chronic disease of the mucous membrane, that calculi are formed. In accordance with this, calculi are rare in the bladder of herbivora, which discharge alkaline urine, and therefore always mixed with a large proportion of a deposit of earthy phosphates.

Carbonate of calcium is met with in some urinary concretions, but very rarely. The above observation of Prout illustrates the circumstances under which it may occur. It is a regular ingredient of the urine of herbivora. I have examined prostatic concretions consisting nearly entirely of this substance. But it is always questionable whether the calcium or carbonic acid were in any case derived from the urine.

CHAPTER XXXI.

IRON.

HISTORY AND LITERATURE.

THE discovery of iron as an ingredient of organic tissues and fluids is more than a century old. It was made by Menghini, a physician of Bologna, upon human blood, and described in a memoir contained in the Transactions of the Bolognese Academy. The extension of chemical inquiry subsequently showed that the food of man and animals always contains a supply of this metal as an accidental admixture or a normal ingredient. For not only was iron found in the flesh and blood, and even the bones, of all animals, but it was also ascertained to be an essential element in the economy of plants, and to be contained particularly in their seeds. It was in consequence searched for and found in the excretions.

Occurrence.

Iron occurs in urine in peculiar forms of combination, which do not reveal the presence of the metal by the direct application to the urine of the usual reagents for iron. The iron compounds must therefore, by some means or other, be extracted from the organic matters with which they are mixed. This isolation is effected with the greatest certainty, by the destruction of all organic matters, in the manner to be described below.

But under accidental circumstances, after the ingestion of soluble iron salts into the intestinal canal, a portion of the salt may pass into the urine, and there become accessible to the ordinary tests for iron applied to the urine directly. Under these conditions the amount of iron present is slightly increased. Compounds in which the iron is contained in the same manner as in the ferrocyanides pass through the circulation entirely unchanged, or only slightly changed, namely, reduced. The recognition of these compounds which do not naturally occur in urine will be discussed under the head of urophanic substances.

Mode of Obtaining Iron from Urine and Determining its Amount.

From 500 to 1500 c.c. of fresh urine are evaporated with the greatest precaution against the accidental admixture of extraneous particles of iron. When reduced to one-tenth the fluid is filtered and again evaporated on the water-bath to the consistence of a thin syrup. This syrup is now introduced drop by drop into a heated platina capsule and charred. When the capsule is nearly full of charred matter a few drops of concentrated nitric acid are poured upon it. A reaction ensues, which, as soon as the platinum becomes red hot, terminates with the complete deflagration of all carbonaceous matters. When all the syrup has thus been gradually charred and deflagrated with nitric acid, and the operation has been completed by the addition and driving-off of a slight excess of the nitric acid, a white, fused, saline mass ultimately remains. It is slowly soluble in water, quicker in hydrochloric acid, under effervescence. It contains carbonates, phosphates, sulphates, and chlorides of potassium, sodium, calcium, magnesium, and iron. The solution in water contains only vestiges of iron; most of this metal remains insoluble in a grey residue containing a little platinum, phosphates of earths and of iron. This residue is treated for some time with hydrochloric acid, and the solution is added to the saline solution. After filtration the mixture is treated with ammonia and sulphide of ammonium. A grey precipitate, which is scarcely ever black, is a mixture of sulphide of iron and phosphates of earths. The precipitate is isolated by filtration, washed, dissolved in a little hydrochloric acid on the filter; the filtered solution is neutralised with carbonate of sodium until a precipitate begins to become permanent; acetic acid and acetate of sodium are now added in small quantity, and the mixture is boiled. The precipitate which forms contains all the iron and some phosphoric acid, but no earths. It is filtered and washed, redissolved in hydrochloric acid, and this solution now yields the characteristic tests for oxyde of iron. The quantity of iron contained in it may be ascertained by the volumetrical method to be described below, or by weighing the phosphate of iron precipitated from the solution by phosphate of sodium, after the addition of acetate of sodium.

Chemical Properties.

Iron as extracted from animal parts, in particular the urine, is obtained in the form of oxyde, Fe_2O_3 , At. W. = 160. While the ashes of blood or its colouring matter have a red colour, being that of the oxyde of iron, the ashes of urine are never red, as the amount of iron present is too small.

The red oxyde of iron is unchangeable by heat. It dissolves completely in hydrochloric acid. Its solutions have a yellowish-brown or brownish-red colour, and when they are neutral as nearly as possible and dilute are decomposed by boiling, depositing the whole of the oxyde of iron. In case the solution contains any phosphoric acid, it passes into the precipitate. From its solutions the oxyde is precipitated in the form of hydrate by caustic and carbonated alkalies. The presence of organic matters, such as are contained in urine, prevents this precipitation. Phosphate of sodium precipitates white phosphate of iron oxyde, which is insoluble in acetic acid. This acid therefore affords the means of separating the phosphates of earths from the iron phosphate. Ferrocyanide of potassium produces a precipitate of prussian blue, which is decomposed by caustic potash, yielding hydrated iron oxyde and ferrocyanide of potassium in solution. Tincture of galls produces a bluish-black precipitate in salts of iron oxyde. In healthy urine, however, tincture of galls produces no reaction. Sulphocyanide of potassium produces a blood-red coloration without precipitate in iron solutions, which is not destroyed by hydrochloric acid.

Volumetric Method of Determining the Quantity of Iron in Urine.

When a solution of suboxyde of iron in an excess of hydrochloric acid is mixed with a solution of permanganate of potassium, the suboxyde is transformed into oxyde, and the permanganate reduced to manganate. One molecule of permanganate of the composition $Mn_2O_7 + K_2O$ yields 5 atoms of oxygen, and thereby transforms 10 molecules of suboxyde of iron into oxyde. A solution of permanganate of potassium of known strength, therefore, may serve to determine the quantity of iron contained in any solution in the form of suboxyde, if added in a quantity just sufficient to effect the oxydation. This quantity may be accurately determined by the loss of colour which the permanganate undergoes as long as it is continued to be reduced; but a single drop of this fluid which is added, over the quantity necessary for effecting the transformation into oxyde of the whole of the suboxyde present, imparts to the mixture a light red colour, which indicates the completion of the analysis.

Preparation of the Standard Solution of Permanganate of Potassium.—We dissolve crystallised permanganate of potassium in a quantity of water, and determine the strength of a given volume of this solution by the following *standard solution of ferrocyanide of potassium*:—7.543 grm. of pure, crystallised, dry ferrocyanide of potassium, containing 1.0 grm. of iron, are dissolved in so much water that the solution exactly amounts to one litre. 10 c.c. of this solution contain exactly 10 milligram. of iron. 10 molecules of

ferrocyanide of potassium require 1 molecule of permanganic acid to be transformed into 5 molecules of ferrocyanide of potassium.

Of this solution we now take 10.0 c.c., containing 10 milligram. of iron, dilute it with about 50 c.c. of water, acidulate with hydrochloric acid, and after having placed the beaker upon a piece of white paper, we add the solution of permanganate of potassium to the solution of iron, which latter is kept in a rotating motion. The appearance of a yellowish-red colour indicates the completion of the test. Supposing the 10 milligram. of iron contained in the 10 c.c. of solution of the ferrocyanide required 20 c.c. of the solution of permanganate of potash for complete oxydation, 1 c.c. of the latter fluid would correspond to $\frac{0.010}{20} = 0.5$ milligram. of iron.

The strength of the solution of the permanganate of potassium may also be determined by the solution of chloride of iron of known strength described under phosphoric acid, or by the solution of oxalic acid of known strength, described under the analysis for phosphate of calcium. By calculation it may easily be adapted to the atomic weight of iron.

Application to the Urine.—The iron isolated from a quantity of not less than 24 hours' urine by the process above related is dissolved in hydrochloric acid and reduced to the state of suboxyde by dissolving in it some pure zinc. It is now freed from the excess of zinc and other matters by filtration, and diluted to the bulk of about 20 c.c. The solution of permanganate of potassium of known strength, as determined before, is now added to the solution of iron, and mixed with it by agitation until the red test appears.

The disappearance of the red colour test after standing a little while, is due to further changes not in connection with the analysis, and need not, therefore, be regarded by the experimenter.

Indications of Iron in the Urine.

The amount of iron obtained from the urine discharged by a healthy man in 24 hours is very small. When dissolved in the form of chloride in an ounce of water it does not impart any colour to the fluid. Divided into four parts this solution will just be sufficient for the production of four qualitative tests with the reagents necessary to prove the presence of iron.

As long as it was believed that the colouring matter of the urine contained iron as an essential elementary ingredient, the iron to be obtained from urine was looked upon with particular interest by physiologists as likely to afford the means for the determination of the amount of urinary colouring matter excreted by the kidneys, and of the quantity of the red colouring matter of blood destroyed in the circulation. But as the colouring matter

of urine does probably not contain any iron, the doctrine just mentioned cannot any longer be maintained. Although iron in the urine has thus to be considered independently of the urochrome, it might nevertheless be derived from disintegrated hematine.

Of the common medicinal preparations of iron none pass into the urine after having been taken into the stomach. They are mostly transformed into insoluble compounds, and leave the body in the fæces. When they are taken for the cure of chlorosis, only such a proportion of them is absorbed as can be assimilated and held in combination by the blood.

CHAPTER XXXII.

ANATOMICAL ELEMENTS OF BLOOD.

INTRODUCTION.

THE presence of any of the anatomical elements of blood in urine indicates serious lesion in some part of the urinary organs. When blood is mixed with the urine, it indicates a breach of surface: in the kidneys, produced by stasis in the capillaries; in their pelves and the ureters, by mechanical violence of a concretion: in the bladder, by rupture of enlarged veins, ulceration, irritation of a calculus, or malignant disease. The presence of blood corpuscles amounts to a demonstration of the presence of the three elements of blood, for obvious reasons. It is best ascertained by the microscope. The presence of fibrine in any form also admits of anatomical demonstration. But albumen requires chemical tests, which, though of a simple nature, yet must be used with certain precautions, in order not to mislead our conclusions. The presence of fibrine or of albumen may be due to exudation without breach of surface.

Blood, Blood Corpuscles, and Coagula.

When very small quantities of blood are present, it is diffused through the whole mass of urine without much altering its colour. In that case it is necessary to let the urine repose in a white porcelain vessel, or in a glass vessel placed on a white sheet of paper, when the blood corpuscles will collect at the bottom in form of a rusty brownish sediment, not easily to be mistaken for anything else, so that it may serve for the diagnosis, by the naked eye, of even very minute quantities of blood.

If a little more blood is present in the urine, it gives it a dirty, dingy, or smoky hue when diffused, forming a larger rust brown deposit on repose. If the urine is of a low specific gravity at the same time, the corpuscles yield part of their red colouring matter, and the urine assumes the pink colour of flesh washings, or the cold extract of flesh. This pink colour passes through all gradations, until the colour of the urine is almost like blood itself. When blood is effused in any consider-

able quantity at a time from larger blood vessels, such as veins of the bladder, or small arteries opened by a concretion, it then coagulates in irregular, mostly lumpy masses, of a black or reddish-black colour. Though these coagula cannot easily be mistaken for anything else by the naked eye, they may yet present certain variations, according to whether they have been formed in the urinary passages, or after the excretion of the urine. When formed in the urinary passages, as is mostly the case when they are formed at all, they may be retained in the bladder or in the narrow canals leading to and from that organ, thus causing irritation of the bladder, dysuria, stranguria, or retention of urine. When retained in the bladder, they may give rise to concretions. When retained in the bladder for a short period only, and there exposed to the influence of a dilute urine, secreted in consequence partly of the stimulus transferred to the kidneys from the irritated bladder, coagula of blood may give up all their colour and be discharged as colourless lumps of fibrine. Such coagula, modified by a sojourn in the bladder, I have known to be declared fibrinous casts of the urethra. The diagnosis of the presence of blood in all these cases, when at all doubtful, is ensured by the

Microscopical Appearances and Reactions of Blood Corpuscles.

Under a power of 400 diameters, these bodies appear as circular disks, with the edges rounded off. The centre of the disk may be light, and the circumference dark; or on changing the focus the reverse may be the case. Their colour is a light brown or reddish-brown hue. On setting the fluid in which they are contained in motion, their true shape becomes at once apparent: for we see the disk excavated on either side. On adding water to the corpuscles we perceive them to expand; the concavities begin to rise and disappear, and the biconcave disks gradually are transformed into globules somewhat analogous in shape to the globe of the earth—compressed between the two poles. The equator of the blood disks becomes a little smaller by this expansion in the direction of the formerly shortest axis. The central marking, shadow or light, according to the focus, now disappears, and the corpuscles assume the illumination of globular bodies. Under a continued influence of the water they gradually yield their colour to the surrounding fluid, becoming themselves pale, and ever more imperceptible, until at last they seem entirely to disappear. But they do not disappear in fact, for if a concentrated solution of any neutral salt be now added to the fluid in which the corpuscles are invisible, they gradually again become visible, but now are without any colour, and mostly of a corrugated outline, their regular shape being scarcely ever restored.

When the normal corpuscles are treated with concentrated solution of any neutral salt, or with syrup, or with a solution of any neutral organic substance, they immediately become flatter, and the excavations deeper, which is indicated by the central shadow approaching nearer to the circumference. At last they begin to crumple and turn up their edges, which become indented and irregular. The corpuscles now assume the most irregular shapes and outlines; and though they have lost part of their colouring matter, yet they are by far more distinct than at first. If to the solution water is now added in sufficient quantity, they assume their former shape, and under the continued influence of the water undergo the changes before described.

In the caustic alkalies, ammonia included, the corpuscles are entirely soluble; and from this solution they cannot by any means be again obtained. In acetic acid the corpuscles become clearer, expand, and after a time are almost invisible, but do not dissolve. In nitric acid the outline of the corpuscles become darker and thicker, whilst the globules become smaller in circumference. Similar effects are produced by hydrochloric acid and the gastric juice. Acid urine only requires a longer time, otherwise its effects are similar to those of the reagents last named, combined with those of solutions of salt. The irregularities of the margin are frequently of such a nature as to represent granules arranged round a central nucleus. When, however, blood is present in the urine in any quantity sufficient to nearly or altogether neutralise any acidity of the urine, these changes do not take place to that extent, the corpuscles remaining either unchanged, or, when the urine is very watery, only giving up part of their colouring matter, or adhering to each other in rouleaux-like rolls of coins, in the same way as the corpuscles in blood which is not mixed with any urine.

Spectroscopical Diagnosis of Blood in Urine.

In most cases the microscope affords conclusive evidence of the presence of blood. In very rare cases, however, the blood is to be looked for in ammoniacal urine; and then the corpuscles are not easily to be found, as they are too soluble in that fluid, which then merely has a red colour, and coagulates under certain circumstances. In this case, as in all others, the presence of blood may be ascertained by means of the spectroscope. The fluid to be examined is placed in a test-tube before the slit of the spectroscope (or on the tray of the microspectroscope), and if the two characteristic bands of absorption appear in the spectrum, hematocrystalline in some form or other is undoubtedly present. The particulars of this reaction will be described in the following chapter.

Pathological Indications.

Most frequently the presence of blood in urine is a symptom of the first or acute stage of those diseases of the kidney which are caused by the entrance into the blood of a specific poison. The blood then proceeds from the congested and ruptured Malpighian corpuscles, as evidenced by the following data.

The *tubuli contorti* of the kidneys are frequently found full of blood in cases where the urine contained blood during life.

The capsules are also filled with blood, and the Malpighian bodies collapsed.

When the blood thus effused into the tubuli is quickly discharged, either by a continuance of the hæmorrhage or because it is mixed with urine or much serum, it will appear in the urine after emission as diffused blood, and cause the appearances described. But when the blood is effused in masses, so as to fill the entire lumen of the tubule, and is not actively pushed on, it may coagulate in the tubule, and make it impervious, or at a later period may be discharged with the urine in the form of blood cylinders, which, by an admixture of epithelium of the tubuli, and by their form—being that of casts of the tubuli—show their origin in a most unequivocal manner. Together with these cylinders, there are mostly other casts present in the urine, characteristic of the affection of the kidney which produced the hæmorrhage. In some cases the poison producing hæmorrhage from the kidneys is a very tangible one, such as a dose of half an ounce of turpentine. In other cases it is a poison of a more obscure nature, like that of scarlatina; typhus sometimes has a similar effect, and in such cases where much blood has been passed during life, all the tubuli of the kidneys are found injected with blood after death.

In some cases of scurvy and purpura a similar hæmorrhage occurs from the kidneys. When the blood casts remain in the tubuli for any length of time, they become much altered, but may always be distinguished from epithelium by their peculiar yellowish-brown tint, which the epithelial casts have not.

The presence of blood in the urine may indicate ulcerated cancer of the kidney. In this case the quantity of blood may be large or small, and may coagulate in the ureters or in the bladder. In advanced stages of the disease, pus and encephaloid matter is mostly present in the urine, thus characterising the hæmorrhage.

The presence of blood in the urine may be due to the mechanical effects of renal concretions, or to ulcerations set up in the pelves and calyces of the kidneys by these bodies. The most general symptom of gravel in the kidneys is hæmaturia, increased by every kind of exertion. The nature of the hæmorrhage is sometimes ascertained by the presence of deposits in the urine on its being

passed—by the passage of gravel. If the symptoms of renal concretion and hæmaturia are combined with the appearance of pus in the urine, it is probable that ulceration exists in the pelvis of the kidney. In these cases the diagnosis is ensured by the local symptoms.

The presence of blood in urine is indicative of certain diseases of the bladder. In these cases the local symptoms appear to be so well marked that there is not much difficulty in fixing upon the source of the hæmorrhage. Thus hæmorrhoids of the bladder are of a very chronic nature, and appear in periodical fits, like hæmorrhoids *per anum*. I observed such a case for several years. The subject of the observation was a lady. The irritability of the bladder was extreme; it was caused first by the venous congestion. This having lasted a day or two, blood escaped by the urine; clots of different forms and sizes remained in the bladder, or blocked up the urethra, requiring the use of the catheter; sometimes they required manual aid, when they had hardly passed the urethra. Thus, even after the hæmorrhage had ceased for a time, the clots would continue to be passed, and they were the paler the longer after the cessation of the hæmorrhage they escaped from the bladder. This condition would last for weeks, with frequent intervals, during which no hæmorrhage ensued. Gallic acid in large doses always removed the complaint after a time. The patient would be well for months, until a new attack made its appearance. The last attack occurred during a severe illness from scarlet fever, of which the aged patient died.

Stone in the bladder not rarely causes hæmorrhage from that organ; so does chronic cystitis, accompanied by erosion or superficial ulceration. I observed the case of a farmer who consulted me for severe disease of the bladder. He discharged an alkaline, foetid urine, with rags of pseudo-membranes, appearing under the microscope to be made up of fibrine with pus-cells closely embedded; on some occasions he, after severe straining and retention of urine, passed a membranous bag, which, when suspended in water, showed itself to be a hollow membranous sac, a perfect cast of a very small bladder. With these membranes of inflammatory origin he passed clots of blood, and fluid blood mixed with the urine, but altered considerably.

Another form of hæmorrhage from the bladder is due to softening cancerous growths of that organ. This disease is by far more frequent than vesical hæmorrhoids, and its presence is supposed to be indicated by every hæmorrhage from the bladder, in the opinion of some authors, who doubt the occurrence of hæmorrhoids of the bladder.

The differential diagnosis of these cases is established by the collateral and local symptoms of each case, which mostly are so

marked that there is not much difficulty experienced in establishing distinctions. Happily, where it is difficult to distinguish, it is of not much practical importance to do so, as the treatment is directed against the hæmorrhage. Whether, in a given case, this proceeds from cancerous growths or from hæmorrhoids, is indifferent, as gallic acid, or any other astringent, will suit both cases equally well. The different course of the diseases would soon establish a diagnosis. But diagnosis is of far greater importance for the prognosis of a case of this kind; and as the latter is chiefly the service which it is possible to render to the patient, for the purpose of guiding his hygiene, an accurate diagnosis is essential.

This can be effected by the microscope, which, in cases of cancer, mostly exhibits the detritus of the growth in the form of cells, nucleated, round, and caudate, many of them with a brood of young cells enclosed. When the cancer is seated in the bladder it mostly assumes the form termed "*villous*." Such villi are then constantly cast off, and obtained from the urine in the shape of little lumps and loose masses. Magnified, they exhibit an arborescent structure. Their substance is composed of a fibrous material, with many nuclei; but the fibres are mostly so fused with each other as to be scarcely distinguishable. Their surface is covered with a layer of morbid epithelium. This epithelium is probably cast off and renewed very frequently, and may, therefore, according to the rapidity with which this process is effected, present various stages of development. The cells may be large, of irregular shape, spindle-shaped, or exhibit several projections; they may contain a large nucleus, or the cells may be round and small, exhibiting a nucleus and nucleoli. When the process of desquamation is active, the cells are not found, but are supplanted by nuclei, which cover the villi as a dense reddish-coloured layer, and appear as such in the deposits of the urine. In some cases all these various forms of morbid formations may be discovered at the same time, in others they appear at intervals.

The prognosis of all these cases, in the first instance, depends upon the nature of the disease, of which the effusion of blood is a symptom. As far, however, as the prognosis is dependent upon the hæmorrhage itself, we may say that it becomes bad in a direct ratio to the amount of blood discharged, to the time during which hæmaturia continues, and to the severity of the symptoms of irritation caused by the formation, retention, or passage of clots in and through the urinary passages. Of all the consequences of clots, the formation of a calculus round the clot as a nucleus is the most severe, and also the most rare.

CHAPTER XXXIII.

HEMATOCRYSTALLINE AND HEMATINE.

INTRODUCTION.

HEMATOCRYSTALLINE is the substance to which the blood and muscles of animals owe their red colour and main chemical power. In all vertebrate animals it is contained in the blood corpuscles, but in some lower animals, *e.g.*, the common earth-worm, it is dissolved in the serum.

Mode of Obtaining.—Blood freed from fibrine by beating is mixed with a solution of salt, and the blood corpuscles are allowed to settle. They are repeatedly soaked with salt water, and collected on the filter. They are next shaken with ether and water, whereupon the hematocrystalline dissolves in the water, and, after rapid filtration, on exposure to a low temperature, or after the addition of some alcohol, crystallises. By this process crystals can be obtained from human blood and the blood of cattle only with difficulty during strong winter frost. In warmer weather the corpuscles settle very imperfectly, and cannot be sufficiently freed from serum. In this case the red water solution is treated with a solution of basic lead acetate as long as a precipitate ensues. This is removed by filtration, the excess of lead by a little potassium carbonate. To the filtrate powdered potassium carbonate is given until the hematocrystalline separates in grumous flakes. These are separated by filtration, and strongly pressed. The cake is again broken, and mixed with a little watery alcohol, which causes the separation of potassium carbonate in solution. Again strained and pressed the cake may be dissolved in water and precipitated by alcohol, or by alcohol and cold.

Chemical Composition, Formula, and Molecular Weight.

The crystallised hematocrystalline of animals has yielded the following results to analysis :—

	Dogs.	Guinea-pigs.	Geese.
C	53.64	53.85	54.26
H	7.11	7.32	7.10
N	16.19	16.17	16.21
S	0.66	0.39	0.54
Fe	0.43	0.43	0.43
O	21.02	21.84	20.69
P ₂ O ₅	0.91
Alkalies	0.04
	100.00	100.00	100.00

From these data the formula $C_{600}H_{960}N_{154}FeS_3O_{177}$ has been calculated, leading to a molecular weight of 13,280. But we cannot yet absolutely determine this, as the blood crystals retain more or less oxygen in loose combination, like the blood itself, and yield it up in the vacuum, provided they are moist, but retain it the more tenaciously the drier they are. Calculating from the quantity of iron contained in them as unit, we arrive at 13,023 as the molecular weight.

Chemical Properties.

Its watery solution begins to coagulate at 90°, and at 94° deposits all hematocrystalline as a reddish-brown curd. A solution of albumen begins to coagulate at 60, and is completely precipitated at 65°. Hematocrystalline combines with oxygen and, more pertinaciously than with oxygen, with a number of other gases, such as carbonic oxide, nitrous oxide, and hydrocyanic acid. It is peculiarly decomposed by sulphuretted and phosphuretted hydrogen, the latter agent producing a complete disappearance of all particular spectral phenomena. Under the influence of acids, or alkalies and alcohol, it is broken up into an insoluble albuminous body and soluble hematine. Sulphuric acid dissolves the albuminous body, and yields a number of products of the further transformation of hematine, which I have described under the generic name of cruentine. All these products show peculiar and remarkable spectral phenomena. While contained in the blood, hematocrystalline is chemically remarkably stable; it is the last ingredient which undergoes putrefaction; it preserves its colour and spectrum for years in a horribly offensive mixture. This is perhaps mainly the result of the power which it possesses of taking up oxygen from the air, and yielding it again to other matter in contact. Its chemical stability evidently is the main factor in the stability of life.

Spectral Phenomena of Hematocrystalline.

Oxy-hematocrystalline.—When a concentrated solution of hematocrystalline is placed before the slit of the spectroscope, and sun-

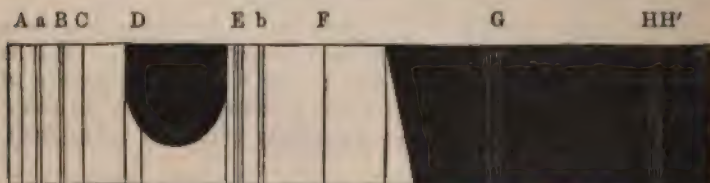
light or lime-light employed for illumination, only some of the most extreme red light is perceived in the spectrum. On continued dilution with water, the illumination extends towards the D line, but before the region of this line has appeared clear, light is perceived in the green between the lines E and F. On continued dilution, the extension of the light proceeds more towards F, and the dark region in the middle of the spectrum,



Intensity Diagram of Spectrum of Oxy-hematocrystalline.

which may now be called a band, contracts but slowly. But it ultimately allows light to pass over its middle, and is soon seen to consist of two bands. Of these the narrower, darker, and stronger defined one is situated towards the red, close upon the D line, while the second wider but pale one is by the side of E. From this point the solution may be greatly diluted, with the effect only of producing some shrinking in the width of the bands. But ultimately they become very pale, and when the solution has ceased to show any colour to the naked eye, the bands also have completely disappeared.

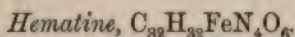
Reduced or Deoxydised Hematocrystalline.—Substances which have a strong tendency permanently to fix oxygen easily change the oxy-hematocrystalline described in the foregoing into the reduced or deoxydised venous variety. Such reducing substances are serum, or serum diluted with water; hydrogen and arseniuretted hydrogen; a solution of iron suboxyde sulphate in ammoniacal tartrate. When a solution of oxy-hematocrystalline has been treated with any of these agents, while protected from contact with air, and placed before the spectroscope, only one broad band is seen in place of the former two. It is a little



Intensity Diagram of Spectrum of Reduced Hematocrystalline.

wider than the two oxy-hematocrystalline bands, including the green space between them, and is moved a little more towards the

violet end of the spectrum. Its intensity decreases more on the violet than on the red side. When the solution is shaken up with air the one band disappears, and the two oxydised hemato-crystalline bands reappear.



Mode of Obtaining.—Amorphous hematocrystalline, produced by pouring blood into a large quantity of concentrated solution of potassium carbonate, is dried at 40° , and extracted with cold absolute alcohol. The ruby-red solution is treated with a solution of tartaric acid in absolute alcohol as long as a precipitate falls down. The filtered solution is then slowly evaporated at 40° , until it deposits all colouring matter as a fine powder of a black, somewhat violet, colour. This, after mixing with water and ether, is made to undergo the previous process once more, whereupon impure hemine is obtained as a violet-black powder, glittering in the sunshine, and consisting under the microscope of rhombic scales, mostly crossed.

This hemine has now to be purified by boiling with benzene and glacial acetic acid, ultimately with glacial acetic acid alone. The solution contains all the impurities, particularly a phosphorised body, and some hematine. The residual powder is dissolved in ammonia, and precipitated by acetic acid. After drying the pure hematine is a black glistening powder, which has the composition expressed by the above formula (Thudichum and Kingzett, "Journ. Chem. Soc." Sept. 1876).

Chemical Properties.—It is insoluble in water, alcohol, and ether, but dissolves in caustic alkaline water, concentrated acids, and in alkaline or acid alcohol.

By keeping it becomes more insoluble in these agents, a part becomes insoluble in all. In its ammoniacal solution salts of earths and metals produce precipitates, which are, however, very unstable. Under the influence of concentrated sulphuric acid it is transformed into a great variety of substances, described as cruentines. During this process it loses much iron, but retains some to the last.

Spectral Phenomena of Hematine.—The alcoholic alkaline solution shows a broad dark band overlying D, as in the diagram.

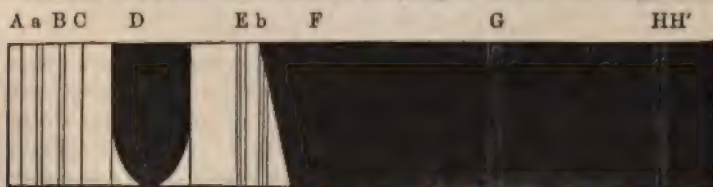


Diagram of Alkaline Hematine in Alcohol Spectrum.

The spectrum is then cut off at the b line. When this solu-

tion is treated with a little sulphuric acid to acidity, sulphate is deposited in crystals, and the spectrum changes to that of acid hematine. This shows four bands of absorption arranged as in the diagram. Pure hematine dissolved in alcohol with a little

A a B C D E b F G HH'

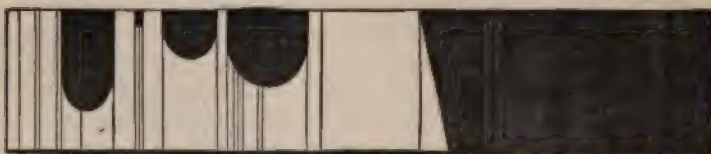


Diagram of Acid Four-Banded Hematine in Alcohol Spectrum.

sulphuric acid gives the same spectrum. But when blood corpuscles precipitated by sodium sulphate are extracted with alcohol and sulphuric acid, as was first done by Lecanu, then a solution is obtained showing five bands distributed as in the following diagram.

A a B C D E b F G HH'



Diagram of Five-Banded Hematine Spectrum.

Reduced Hematine.—When an alkaline watery solution of hematine is mixed with a deoxydising agent, such as the alkaline tartrate solution of ammonio-sulphate of iron suboxyde, the former spectrum gives way to a new one, showing two bands, as in diagram.

A a B C D E b F G HH'

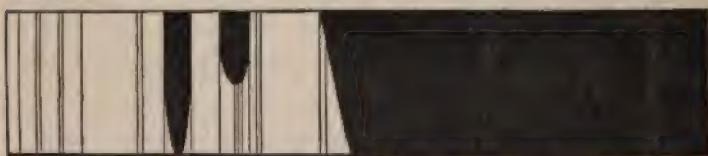


Diagram of Reduced Hematine Spectrum.

The two bands are situated at about the same distance apart as those of oxy-hematocrystalline, and are no less sharp and distinctive. They are a little more removed towards the violet end, and the first band is distant from the D line by about its own breadth. They differ much from the bands of oxy-hematocrystalline in the relative strength of the first and second band. Like hematocrystalline reduced hematine is oxydised by shaking

up its solution with air, the one band alkaline hematine spectrum reappearing.

Influence of Organic Acids upon Blood.—When an organic acid, such as acetic or tartaric, is mixed with diluted blood, one band in red appears, and a great obscuration of the rest of the spectrum ensues. The one band in red belongs to acid hematine, and the darkness in green is due to the two other bands described. These it is not easy to define without the aid of sunlight or Drummond's light. In such watery acid solution the hematine is probably only in a state of suspension; for on standing for some time the whole of the hematine is deposited, and its spectrum disappears from the solution, which, previously thick and not translucent, now becomes perfectly clear. We shall see in the next chapter that some descriptions of morbid urine behave exactly like these mixtures of diluted blood and organic acid.

Cruentine.

Mode of Obtaining.—When hematocrystalline is boiled with sulphuric acid, it becomes chemolysed, the albumen dissolves, while a brownish-red grumous matter remains in an insoluble state. Treated after washing with pure sulphuric acid, it dissolves entirely, and is now cruentine sulphate.

Spectral Phenomena of Cruentine Sulphate.—A concentrated watery solution of this body shows one broad black band in red to orange; the visible blue is about as wide as the visible green, whereupon the spectrum is cut off. On dilution this band splits up into two, and a third very feeble band in green becomes visible just to disappear.

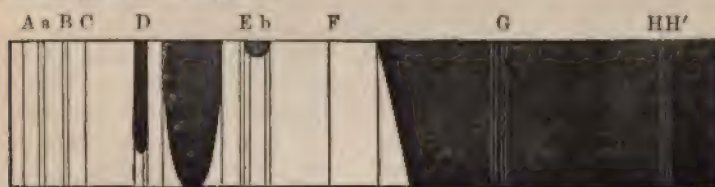


Diagram of Spectrum of Cruentine Sulphate.

This spectrum is remarkable on account of its close resemblance to that of *paramelanine*, described in the chapter on *uromelanine*. From this sulphate of cruentine a great number of other derivatives have been obtained, and described in my several reports of researches, &c., in the 9th, 10th, and 11th Reports of the Medical Officer of the Privy Council.

CHAPTER XXXIV.

CRUENTURESIS.

GENERAL DESCRIPTION.

IN all the cases of this disease, also called intermittent hematuria or hematuria, which have been observed the immediate exciting cause of the attacks has been invariably some definite exposure to cold or wet. The form taken by the attack has invariably been that of paroxysms; these coming on suddenly, almost immediately after the chill was experienced, and passing off rapidly when the effects of the chill had been counteracted and the patient had become thoroughly warm. In every instance the paroxysms have begun with coldness of the extremities, followed by general chilliness, amounting in the severer attacks to rigors. In like manner, in every case, the chilliness or shivering has been attended by a feeling of weight and pain in the loins, and by pain or a sense of weakness or stiffness in the lower limbs. The chilliness has been usually, though not always, followed by an imperfectly marked febrile hot stage. The patients have invariably pains during the paroxysms, urine looking as if it were mixed with blood, and identical in general character. The same definite course has been run by the paroxysms in every case. From half an hour to two hours after the chilliness or rigors the patient has never failed to pass the first dark-coloured urine, which has always been coagulable by heat (hematocrystalline), and has contained numerous crystals of calcium oxalate, with more or less of brownish-red or yellowish-red amorphous granular matter (hematine) and a few hyaline casts, but only occasionally some stray blood corpuscles. At each succeeding micturition after the chilliness the urine has invariably shown more or less diminution of colour, of coagulability, of calcium oxalate, and of its other abnormal constituents; resuming its natural character and appearance by the second or third micturition after slight attacks, and usually by the fourth or fifth after severe paroxysms. By the second day after an attack the patients, as a rule, have regained their ordinary degree of health and strength, and have continued well until some fresh exposure has brought on a new attack of their

complaint. Most of the patients suffering from this disease have had the same pale, sallow, cachectic aspect, two of them having been distinctly "jaundiced," and the others having all had at times an icteroid tint of skin.

Cruenturesis, therefore, is a definite disease due in all cases to the same remote constitutional cause. The only medical treatment which appears to have any effect in diminishing the liability to suffer from the paroxysms on every exposure, is treatment directed during the intervals towards the improvement of the general health and the strengthening of the patient's constitution. Once the paroxysms have set in, the most simple means of restoring warmth are all that it is advisable to use. The short duration of the paroxysms, the very general absence of blood corpuscles from the urine, even at the time of the paroxysms, and the complete recovery of the normal character of the urine within a few hours after their subsidence, seem to show that there can be no cause of hæmorrhage in the kidneys themselves, but rather that the disintegrated blood traverses through the walls of the blood vessels in the Malpighian bodies. For this reason E. H. Greenhow (the author of a learned and instructive essay on this disorder) regards the kidneys rather as the organ of elimination than as the seat of the disease, and considers the renal irritation, the existence of which is manifested by the pain in the loins and by the presence of the casts, and occasionally also of stray blood corpuscles in the urine, to be a secondary affection consequent upon congestion of the kidneys produced by the sudden and unusual strain thrown upon them. Possibly the paroxysms may consist in the sudden disintegration of an unusually large quantity of blood corpuscles, setting free so considerable an amount of hematocrystalline that it cannot undergo the normal changes, but is eliminated through the kidneys in a comparatively unaltered state.

Several authors have considered the disease to be of malarious origin, and there is no doubt that in some of the cases published the patients had also suffered from ague. But on the other hand many cases have never suffered from ague, and some at least have never visited a malarious district. The disease, in fact, merely resembles ague in its intermittent form and in its commencement with rigors, which are followed, however, by only an imperfect hot stage, and rarely by a sweating stage. It differs from ague in not being periodical, and in requiring, apparently, a fresh exposure to cold or damp to excite each separate paroxysm. The history of most of the cases seems clearly to indicate the existence in all the patients of some sort of dyscrasia, upon which the external chill acts only as the immediate existing cause of the paroxysm. Many patients suffer from so-called rheumatic pains during the paroxysms. Some patients suffer

from such pains at all times, but this is probably due to collateral disorders, with which they are afflicted at the same time. No *post mortem* examination has ever been made of any case.

Spectroscopical and Chemical Examination of the Urine.—The urine is of brownish-red colour, and turbid by a brownish-red precipitate. When the latter is filtered off and tested, it is found to be hematine in the same state as the hematine which is precipitated by acetic acid from a watery solution of blood on standing. The filtrate is more red than brown, clear, and port wine red in transmitted light. In layers of from 1 to 2 centimetres in thickness it exhibits before the spectroscope two absorption bands, which on dilution or exposure of thinner layers augment to four, as exhibited in the diagram.

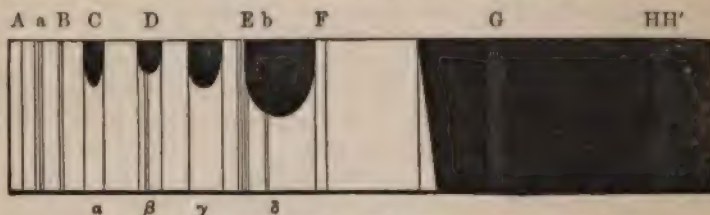


Diagram of Spectrum of Urine in Intermittent Cruenturesis.

At first sight this spectrum offers a remarkable similarity to that of alkaline four-band cruentine described by me elsewhere. It is, however, clear that cruentine cannot be present. By boiling of the urine the entire amount of colouring matter is coagulated, and from the coagulum alcohol and sulphuric acid extracts hematine only. This points to hematocrystalline with the spectrum of which the bands β and γ nearly coincide. It is next found that the bands a and δ coincide with two of the bands of hematine in acid solution. Further, when the urine is treated with a reducing solution of sulphate of suboxyde of iron in tartrate of ammonium with excess of this alkali the four bands immediately disappear, and one broad band is present in their place.

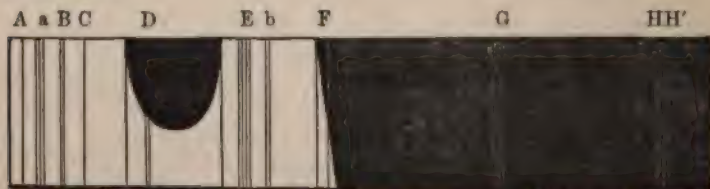


Diagram of Spectrum of Urine treated with Reducing Fluid.

By violent shaking with air the broad band disappears, and the former bands do not always reappear. The fluid is extremely turbid, and most of the hematine and hematocrystalline is pre-

cipitated. Thus far the mixture differs in bearing from pure hematocrystalline and hematine, in which, after reduction and shaking with air, the bands would reappear. From a comparison of the spectrum of reduced hematine it will be seen that it necessarily coincides with that of reduced hematocrystalline, that the separation of its bands cannot appear just as in the original spectrum of the urine the bands 2 and 3 of four-band hematine, or the bands 2, 3, and 4 of five-band hematine, coincide with the two bands of hematocrystalline. All parts therefore show that hematocrystalline and hematine in about equal proportions are present in the urine in question, and the only anomaly which may perhaps yet be explained by the complex character of the fluid is that on shaking with air of the reduced fluid, although the one band disappears none of the original bands reappear. Somehow or other the substances have been changed by this operation.

The paroxysmal urine is extremely acid; the nature of the free acid remains to be examined. On standing it deposits a flocculent brown precipitate of hematine, and the bands of hematine in the spectrum become much paler, while the fluid becomes redder. Watery blood, mixed with a little acetic acid shows the same bearing.

From all observations it follows that the urine in paroxysmal cruenturesis contains hematocrystalline and hematine in solution. The hematine also occurs as a precipitate, which increases on standing. There is no proof of the presence of dissolved albumen apart from the coagulable hematocrystalline. It is probable that in this disease a small quantity of blood is somehow or other dissolved, *e.g.*, by bursting of a Malpighian glomerulus, and mixing of the blood with effused urinary water, or by other means. The hematocrystalline so effused is in part transformed into hematine (and some other body, possibly albumen in a precipitated flocculent form), which for a time remains in the fluid, but is gradually deposited in the insoluble form. This transformation is probably due to the morbid evolution in a certain part of the kidney of a quantity of organic acid, possibly acetic, or kryptophanic acid, which dissolves the hematine, and imparts to the urine an unusual and very high morbid degree of acidity. The presence of oxalate of calcium in the urine is no anomaly, but if it has any significance by being present in large quantity would point in the same direction, as the presence of an excess of the other acids. The presence of acetic and kryptophanic acids is no anomaly, as they are normal ingredients of the urine. But their presence in a concentrated form in a certain part of the kidney tubes, where the other urinary constituents, notably urea, were not yet secreted and mixed with the hematocrystalline solution, so that it could transform a part of the effused hema-

to crystalline into hematine, is a great anomaly, and perhaps the essence of the disease. Possibly the acid itself is the cause of the effusion of the blood, of its solution and partial transformation.

My observations on cruenturesis were the first instance in which hematine, hitherto known as an art product of the laboratory only, has been proved to be present in an organic morbid fluid as the product of the diseased process itself.

Cruenturesis after Breathing Arseniuretted Hydrogen.

A professor of physics having performed an experiment with a balloon full of hydrogen, breathed some of this gas, when emptying the balloon of its contents by pressure. He became suddenly very ill, but soon recovered, and after the lapse of some time passed a urine which was black like ink, coagulated on boiling, but contained no blood corpuscles when examined under the microscope. This condition of the urine lasted for about twenty-four hours. It was found that the hydrogen used for the experiment contained arseniuretted hydrogen (J. Vogel).

In a similar case related by Schindler, a deep reddish-brown urine, mixed with clots of blood, was discharged. In the case related by O'Reilly, there was first bloody urine, succeeded by suppression of urine, after which the face became copper-coloured, and the rest of the body greenish, symptoms probably indicating the presence of free hematine in the blood. As matters stand at present it is impossible to decide whether the hematocrystalline is not free in the blood already, or after blood has extravasated. Blood might enter the kidney tubes, form casts, and then be extracted by urinary water. The casts might be, as they sometimes are, expelled after having been quite deprived of colouring matter. On the other hand, the symptoms of hematogenetic icterus are more easily explained by a dissolution of hematocrystalline within the blood; they could, however, also result from a reabsorption of effused hematocrystalline from the kidneys; the process would be similar to the absorption of effusions in bruises.

Vogel caused a dog to breathe arseniuretted hydrogen, whereupon the animal discharged a blackish-brown urine, which contained a large amount of hematocrystalline.

Cruenturesis in Typhus.

In Typhus blood is not rarely discharged from the kidneys. Sometimes, however, the urine shows the features of cruenturesis, hematocrystalline alone, without any visible blood corpuscles being present. This happens during the acme of the disease, and disappears after some time.

CHAPTER XXXV.

URORUBROHEMATINE AND UROFUSCOHEMATINE.

HISTORY AND LITERATURE.

THESE morbid pigments were first described by J. H. Schultz (case of pemphigus leprosus, complicated with lepra visceralis, "In. Diss. Greifswald," April 1874), and F. Baumstark (two pathological urinary pigments, Pflüger's "Archiv." 9 (1874), 568).

History of the Case.—A wandering artisan was in June 1860 seized with general indisposition, which returned every spring in an aggravated form until 1873, when he died. The attacks began in April or May with violent fever, during which the temperature of the body sometimes rose to 41.0° C., and lasted until September or October. The fever seemed to be a daily ague, with cold and hot stage, but without perspiration. The spleen was increased during each period of sickness. He was treated during 1870 with injections of arsenic, and in 1872 with injections of secale cornutum. In 1873 he became ascitic, and had to be tapped twice shortly before his death. The ascitic fluid evacuated in the first operation measured 3800 c.c., was yellow and albuminous, and strongly acid. The heart and digestive organs were not affected. At each period of sickness, after the fever symptoms had continued some time, blisters rose on the skin of the patient, which when pricked effused a sanguinolent fluid, strongly acid and containing pigment cells in suspension. These blisters then became purulent, and casting off the epidermis were transformed into ulcers, which healed but slowly. The first blisters appeared in 1860 upon the nose. At later periods they extended over the entire head, the nape of the neck, and ultimately the fingers. The extremities, abdomen, chest, and back remained free. The blisters again attacked the nose in 1866, and left for the first time a cicatrix upon that organ. After this the nose and both ears were entirely destroyed, and the fingers became affected. During the winter months the patient appeared to be in ordinary good health.

Some years before the appearance of the skin complaint the patient had observed his urine to be red, darker in the morning, lighter towards evening. The colour became more intense with

the progress of the disease. In June 1871, and in July 1872, when the pemphigus was extremely developed, the urine was observed to be dark or black. The specimens of urine which yielded the pigments to be described below were observed during March 1873.

From the clinical observations of the patient it appeared that during the periods of sickness and increase of spleen, the colouring matter of the blood became much diminished, a circumstance which led the observers to lay the focus of the disease into the spleen. They conclude that the chemical process in the spleen by which, according to a current opinion, the normal red colouring matter is formed, was so far altered by the disease that the abnormal pigments to be described below were formed instead.

The patient's appetite was good, and his digestion regular. Yet he was emaciated and weak.

At the *post mortem* examination the spleen was found much increased in size, 9 inches long, $5\frac{1}{2}$ inches broad, and $2\frac{1}{2}$ inches thick. Beyond this increase no pathological features were discovered about the spleen; its colour was brownish-red, nearly black, and this is supposed to have been due to a deposition during the illness of some other undefined abnormal pigment. The kidneys were small, their capsules easily detached. On sections there appeared no anomalies, except remnants of hæmorrhagic spots in the cortical and central substance. The authors do not believe that there was any connection between these conditions of the kidneys and the pigments of the urine.

The urine of the patient was observed in hospital from August 1869 to August 1870 as regards quantity and specific gravity. The greatest quantity was 2620 c.c. in twenty-four hours; the smallest, 1130 c.c.; mean, 1875 c.c. The specific gravity was maximum, 1019; minimum, 1009; mean, 1014. In 1872, during the most severe paroxysm of the disease, on June 19, the urine amounted to 1870 c.c., and was of specific gravity 1009.

Baumstark examined the urine for the first time in March 1873, when the patient was relatively well, and found it of a fine red colour like claret. In June 1873, when the patient was again very ill, other specimens were examined, and found to be brownish-red, sometimes nearly black, so that they had to be diluted to show their true colour. As the case proceeded towards its termination the colour of the urine became more brown, and the last urine passed on the day before death was of a purely coffee-brown colour. The odour of the urine was strong and peculiar, unlike normal urine. When heated with alkali it emitted a faecal odour. The peculiar odour adhered to all preparations made from it almost to the stage of ultimate purity. The reaction of the urine was always strongly acid.

When fresh it was always clear and transparent, and under the microscope no formed ingredients except a few granules of amorphous pigment could be found in it. In particular, blood corpuscles, which were carefully searched for, could never be found. It never contained albumen, never any biliary colouring matter. It made a strong deposit, which seems to have consisted of urates at earlier stages; later on Baumstark found it to consist of uric acid. Almost the half of the uric acid contained in the urine fell out spontaneously when it was allowed to stand forty-eight hours. The average quantity of urea contained in the twenty-four hours' urine was 29.5 grm.; of uric acid, 1.6 grm.; of phosphoric acid, 2.2 grm.

The spectroscopic examination of the urine showed two feeble absorption bands, a narrow one lying near D towards the red, and a wide one, lying away from D one-third towards E. From E towards the violet there were different shades, which Baumstark does not define any better, though he indicated them in his sketch. The pigment was very stable. It was precipitated by basic lead acetate.

Isolation of Two Colouring Matters.—The urine was subjected to dialysis. A fluid of the yellow colour of normal urine, together with the salts, passed through the dialyser, while a brown mud remained deposited on the membrane. This mud was easily soluble in caustic soda, and the solution on addition of acid deposited brown flakes, while another pigment of magenta-red colour remained in solution. When the brown deposit was filtered off, and the red acid filtrate was again subjected to dialysis, the red pigment also was deposited in flakes. By frequent repetition of these proceedings, both pigments could be perfectly separated. But it was necessary to frequently change the water under the dialyser. If the water became too salty, the pigments also passed through the membrane. To avoid all loss the dialysis was allowed to complete itself into a current of water running slowly under the diaphragm. The brown matter was termed by Baumstark *Urofuscohematine*, the red pigment *Urorubrohematine*. The red urine in March 1873, and for some time after, contained mostly the red pigment; towards June the brown pigment began to prevail, and ultimately was the only abnormal pigment present, the red one having almost entirely disappeared. The urine of twelve days yielded about 2 grm. of mixed pigments; from the mixture there was obtained more brown than red pigment.

Urorubrohematine.

The analyses of the pigment gave the following results:—

C	50.87	N	6.57
H	5.89	Fe	7.30

From these figures Baumstark calculates the formula— $C_{65}H_{94}N_8Fe_2O_{30}$, which he assumes to be derived from hematine by the substitution of 8H by 4O, and the addition to the molecule of $16H_2O$. Considering that the formula of hematine upon which this formula is based has been proved to be wrong (*see* above, Hematine, p. 355), and that it is not certain whether there was not some inorganic acid combined with the urobromohematine, this formula is very improbable.

The freshly precipitated pigment is a flaky dark brown mass, easily separated from the liquid by filtration. Dried over sulphuric acid, it is a bluish-black mass without lustre. It was never crystalline. On paper it makes a nut-brown mark; it is very light. It is insoluble in water, alcohol, ether, chloroform, benzol, carbon sulphide, solution of common salt. It is soluble in alkalies, including ammonia, with a brownish-red colour, which on dilution becomes granate, without dichroism, in phosphates and carbonates of alkalies, with a light red colour. In those solutions acids cause no precipitate, but a change of colour to a bluish cherry-red. When the acid solution is subjected to dialysis, the pigment is completely precipitated before the liquid has lost its acid reaction.(1) When the acidified solution is evaporated to dryness, the pigment becomes completely insoluble in water. The alkaline solution, however, can be evaporated in the water-bath without undergoing any visible change. Calcium and baryum salts do not precipitate the pigment from such alkaline solutions. Hydrochloric acid much diluted with water, or with alcohol, dissolves the pigment with a violet colour. Solution of sodic chloride, with some hydrochloric acid dissolves it with a cherry-red tint. The acid solution before the spectroscope shows the principal bands of the original urine, namely, a narrow band on the side towards red of D, and a broad band between D and E, nearer to D. (This is exactly the acid cruentine spectrum originally described by me in Rep. 1867, *see* above under Cruentine, p. 357. Baumstark in his sketch omits to draw the terminal absorption towards the blue.) The alkaline solution Baumstark describes as showing four bands, of which one, however, is the terminal absorption from G to H, which in the previous spectrum he has neglected. It is therefore more correct to say that this alkaline solution had three bands, of which one, narrow, was near D towards E, another equally narrow overlying E, and a very broad one stretching from F to half-way towards G. Then there was a blue interval, and the rest from G was black, without any violet being visible. (This spectrum does, however, not coincide with my four-banded spectrum of alkaline cruentine, in which four detached bands are all distributed between D and F.)

Urofuscohematine.

This pigment yielded on analysis—

C	.	.	.	55.95
H	.	.	.	7.41
N	.	.	.	7.68
Fe	.	.	.	0.14

and is declared by Baumstark to be a hematine free from iron, in which iron is replaced by 4H, and to which 16H₂O are added, an operation which yields the formula C₆₃H₁₀₉N₅O₂₆. To this formula also the remarks apply which I made when speaking of urorubrohematine.

Freshly precipitated, it is flaky dark brown, dries over sulphuric acid to a black shining mass, makes a dark brown mark on paper, insoluble in water, alcohol, ether, chloroform, benzole, acids, and in solution of common salt, containing free hydrochloric acid. Soluble in alkalies with a brown colour, without dichroism; not altered by dilution, and precipitated from this dilution by acids in brown flakes. From the alkaline solutions it is precipitated in brown flakes by calcium and baryum salts. In phosphates and carbonates of alkalies, and in alcohol containing hydrochloric acid, the body dissolves with a brown colour. Spectroscopically, the body is not well characterised. Its alkaline solution shows a shade between D and E, another very faint one, difficult to recognise between b and F, overlapping F; violet and blue strongly absorbed; the entire spectrum very diffuse, and badly defined.

Both bodies are described as very stable, so that they can be boiled with concentrated caustic soda or hydrochloric acid for some time without suffering any change. Heated with soda lime, they yield the nitrogen as ammonia. A quantity of a product, smelling like tar, passes over at the same time, with other brown empyreumatic products. When subjected to dry distillation by themselves the pigments evolve a disagreeable odour, and yield a product which in small quantities even yields the reaction for pyrrol (deposits pyrrol-red, colours a pine-shaving moistened with hydrochloric acid of a red colour). This result is similar to that obtained from hematine.

There can be no question that these bodies are related to hematine, and that they are perhaps derived from it. They are characteristic products of rare, chronic, severe, and fatal forms of constitutional disease.

CHAPTER XXXVI.

FIBRINOUS, LYMPHATIC, OR CHYLOUS URINE.

HISTORY AND LITERATURE.

THE condition of urine here referred to was first described by Prout ("Stomach and Urinary Diseases," 3d edit. p. 112). A series of observations were given by Bence Jones ("Medic. Chir. Trans." 33 (1850), and "Phil. Trans." (1850) 2, 651, and some cases described by Elliotson ("Med. Times and Gaz." Sept. 19 (1857), p. 288). The anatomy of a case has been recorded by Priestley ("Edinb. Med. Jour." 1856, p. 945). A great number of sporadic observations throw no light either on the etiology of the disorder or on the chemistry of the urine, and need not therefore be quoted (*see* Schmidt's "Jahrbücher," 1863, 12, 274).

Fibrine.

Fibrine is anatomically well characterised by its spontaneous coagulation. Of its chemical properties little is known, if we except the percentic elementary composition, which is almost identical with that of albumen and caseine.

When fibrine occurs in urine it always coagulates at some time or other after having left the circulation. It may become insoluble already in the urinary tubules, and then constitute the various descriptions of casts of those tubules—the common products of certain diseases of the kidneys. In other cases, not absolutely connected with diseases of the kidneys, the fibrine may be kept in solution in the urine until its arrival in the bladder, and then coagulating, may give occasion to difficulty in passing the urine. It may also keep in solution until the urine has stood for a time after its emission, and then coagulating, may assume the shape of the vessel in which it happened to be at the time.

When such coagulating urine contains fat in appreciable quantities, and is thereby made turbid and opaque, like milk, it is termed chylous urine. This coagulating or chylous urine establishes a very different prognosis from urine containing fibrine in casts, or in large coagula assuming the shape of the

vessel formed after emission, and denoting acute disease of the kidneys.

Chylous Urine.

This description of urine is of very rare occurrence in Europe, about half the number of cases on record having been observed in natives of hot climates (East and West Indies, Mauritius, and Brazil), or in individuals who had resided for many years in hot climates.

The properties of chylous urine are due to the admixture with healthy urine of certain constituents of the blood, or lymph or chyle, which admixture is itself the effect of some peculiar disease at present unknown, but what may be surmised to be probably of parasitic origin. The urine which is secreted under the influence of that disease is characterised by the presence of either, or several, or all of the following abnormal ingredients:—

Red blood corpuscles, frequently mixed with some white ones. They may be entangled in fibrinous coagula, or form a deposit on standing. In either case they are easily diagnosed by the microscope.

Fibrine occurs in shreds and films, enclosing blood globules, which rise to the top of the fluid on standing, and remain on the filter, through which the urine may be passed. Blood globules frequently pass through the filter. When the fibrine occurs as a single coagulum, it may be small and partial, and occupy the centre of the vessel as a contracted mass, like the coagulum of the blood in its serum. On other occasions the whole of the urine, already in the bladder, or in the vessel into which it has just been passed, coagulates into a tremulous mass, which, when fatty, is like white jelly, and assumes the shape of the vessel.

The coagulum, in both instances, particularly if it be broken up by agitation, gradually separates into two portions—a fluid or serous portion, more or less opalescent or milky, like the urine itself, and which, when left at rest for a few hours, frequently throws up a sort of creamy matter on its surface; and a very delicate fibrinous mass, small in comparison with the original bulk of the coagulated mass, of a flesh-like appearance, and generally tinged more or less of a red colour, from the presence of blood corpuscles.

Albumen may be present in very small or very large quantities. It is then demonstrated by the usual tests—boiling and nitric acid. The amount of albumen was found by different inquirers performing nine analyses to vary between 0.2 and 1.9 per cent. of the urine.

Albuminoid matter—imperfect albumen of Prout—I have met with in apparently normal urine of a patient who ordinarily excreted chylous urine.

The urine gave no reaction for albumen, but yielded an abundant precipitate with tannic acid. This acid does not produce any precipitate in healthy urine. The albuminoid matter was not gelatine, as it did not gelatinise when the urine, after evaporation on the water-bath, was allowed to cool. This matter resembles alkali-albumen, or caseine, in that it does not coagulate on boiling, and remains soluble in boiling water after evaporation of the urine to dryness.

Fatty matters.—Their presence is the cause of the milky turbidity which may exist in all degrees from a pale opalescent white or amber, permitting the transmission of some light through layers not exceeding an inch in thickness, to milk-white, and quite impervious to light.

In this description of urine there are seen floating under the microscope myriads of infinitely minute particles; globules of oil are only rarely met with. The minute particles are scarcely recognisable under a power of 420.

This milky urine, when digested with its bulk of ether, on repose yields three layers—an upper ethereal solution, beneath this is a thin filmy layer of albumen precipitated by the ether, and lowest the now almost perfectly clear urine, containing some ether in solution. The upper ethereal solution, after the ether has been removed by distillation, leaves the fatty matters.

These consist of a mixture of fats and fatty acids. The fats can be separated into two portions, one solid, the other liquid, at the ordinary temperature, by pressure between folds of bibulous paper, from which the oily fat can be again extracted by ether. The presence of a free fatty acid can be shown in two ways: first, by extracting the fats with strong alcohol, and adding some alcoholic lead acetate, when a precipitate of an insoluble lead salt will ensue (probably stearate); secondly, by boiling the solid fat or a portion with solution of sodic phosphate. A white emulsion indicates the presence of fatty acid. When the liquid fat is boiled with phosphate of sodium, a slight emulsion is also obtained, due to some fatty acid dissolved in the oil; but the oil on repose collects again on the top of the solution in the shape of the same drops in which it had been added. The oil, with sulphuric acid and sugar, gives a purple reaction, though never strongly, caused by the oleic acid, which may be present in the free state or as oleine. The fat extracted by ether from urine or its residue by evaporation always contains a quantity of reddish color and strongly smelling oily matters, from which it can be extracted by strong alcohol; but when the fats are removed, a white crystalline mass appears. Eggel has reported (1870, p. 121) a case of chylous

could extract by ether matter weighing 2.68 grm. In these he believes to have shown the presence of neutral fats, fatty acids, cholesterine, lecithine, and even of the products of decomposition of the latter, neurine and phosphoric acid. Ackermann ("Deutsche Klinik," 1863, Nr. 23 and 24) denies the occurrence of fatty acids. Beale found in the chylous urine of a woman so much as 13.9 grm. of fats per litre; Quevenne, 19.0 grm.; Bouchardat, 13.6 grm.; Rogers, 11.0 grm.; Edwards, 9.9 grm.; Bence Jones, 7.9 grm.; and Gamgee, 2.0 grm. per litre.

Variations in the Nature of the Secretion.

The urine is oftener fatty when the patient subject to this disease lives on an animal diet than when he eats a more vegetable one. It is most clear before breakfast, and most fatty after dinner. It is oftener free from fat before breakfast, when the diet is vegetable, than when it consists more of animal food. Fat passes off in the urine after food is taken, yet the albumen and fibrine and blood globules are thrown out before any food has been taken. During perfect rest the albumen ceases to be excreted, and it does not appear in quantity in the urine even after food is taken, provided there is perfect rest. The disease of the kidneys permits fibrine, albumen, globules, and salts to pass whenever the circulation through the kidneys is increased; if, at the same time, fat is present in the blood, or chyle, it escapes also into the urine. A short time after rising early the urine may coagulate spontaneously, although no fat is present in perceptible quantity, and this may happen before any food is taken. More frequently, however, the urine coagulates after food, and when fatty at the same time. The albuminoid substance is present in urine containing neither fibrine, nor albumen, nor globules, nor fat; in short, in urine which, without the test of tannic acid, would have the chance of being considered perfectly normal.

The *prognosis* of these cases is favourable, in so far as the disease may last for a long time without terminating the life of the patient. But his sufferings are great and variable.

Hypothesis regarding the Cause of Chylous Urine.

An analysis of a great number of cases, and more particularly of the best observed cases, leads to the conclusion that the abnormal ingredients of the chylous urine have not passed from the blood through the kidneys together with the other normal ingredients of the urine, but have passed from some part of the lymphatic system or thoracic duct, through an anomalous channel, or permanent fistula, to the pelvis of the kidney, to the ureter, or the bladder (Carter, "Med. Chir. Trans." 45, 189). When I mixed fatty serum from venous blood with healthy urine in certain

proportions, I obtained a liquid which could not, by either aspect, or chemical or microscopical analysis, be distinguished from the ordinary chylous urine of a patient whose secretion I had an opportunity of examining for many months. The nature of the liquid would therefore be explained perfectly by the existence of such a communication between the carriers of lymph and chyle and the urinary passages. The formation of the fistulous communication has been conjectured to be possibly the result of the destructive operation of some parasite, whose seat by choice is the lymphatic system of the urinary passages (Roberts). This hypothesis seems to me to be more plausible than any other, and should be carefully borne in mind by those who may hereafter have opportunities for anatomical investigation.

Fibrine, the Produce of Acute Disease of the Kidneys, Coagulating after Excretion.

This description of fibrine is essentially a symptom of acute desquamative nephritis. It is therefore mostly mixed with a little blood, but the amount of fibrine is so large that there can be no question as to its being due to exudation and not to hæmorrhage.

A case of this kind was observed by Vogel. The urine of a woman labouring under Bright's disease was found, for a length of time, to form a pale pink-coloured coagulum of fibrine at the bottom of the vessel regularly a few hours after emission. The coagulum contained numerous pus corpuscles and few blood corpuscles; the latter being so scarce that the blood which they represented could never have yielded the entire amount of fibrine.

The indications of the coagula of fibrine being the produce of well-marked acute disease of the kidneys are not very well known, as the number of cases of this kind hitherto observed has been too limited to admit of general deductions.

CHAPTER XXXVII.

ALBUMEN.

HISTORY AND LITERATURE.

THE connection of certain forms of dropsy with the presence of coagulable albumen in the urine, and of the latter with kidney disease, was first pointed out by Bright ("Reports of Medical Cases," 1827). The albumen was traced to the blood, and the urine containing it termed "serous." The fact that different descriptions of albuminous substances occur in urine is a much later acquisition.

Occurrence.

Albumen is formed in plants, and introduced into the animal economy as food; it there undergoes certain modifications, serves the purposes of the economy, growth of organs, and production of power, and becomes disintegrated, leaving the body mostly in the form of urea. But when albumen, as such, is discharged in the urine, this is a sign of severe disease of the blood or of the kidneys.

Chemical and Physical Characters of Albumen.

Albumen occurs in a soluble and an insoluble modification. The former is present in all the fluids of animal and vegetable bodies, and may be transformed into the latter by boiling with water, or by contact with absolute alcohol, acids, or alkalies. The soluble modification may be obtained in a solid state by evaporating the solution at a temperature not exceeding 50°, or by drying *in vacuo* over sulphuric acid. It is a yellowish transparent mass, of 1.314 specific gravity, which swells up with water, and after a time dissolves. It has an alkaline reaction, and contains about 5 per cent. of free alkali and salts, which may be partly removed by washing with water, as they dissolve quicker than the albumen itself. The albumen thus freed from alkalies is insoluble in pure water.

The insoluble modification of albumen is a flaky or lumpy mass, without taste or smell, insoluble in water, alcohol, and ether, soluble in dilute caustic alkali by the aid of a gentle heat, from which solution it may be precipitated by the ad-

dition of an acid. The precipitate is changed in some degree, having lost part of its sulphur, which is sometimes evolved in the form of sulphuretted hydrogen. The insoluble modification is also soluble in concentrated acetic acid and common phosphoric acid; and in these solutions a precipitate is produced by ferrocyanide and ferricyanide of potassium. It is soluble in *very dilute* mineral acids, or at least is transformed into a jelly-like mass; the addition of a larger amount of acid to these solutions produces a precipitate. Concentrated hydrochloric acid, or sulphuric acid somewhat dilute, or a mixture of concentrated hydrochloric acid and some sulphuric acid, dissolve the insoluble modification of albumen formed by the aid of heat, and decomposes it. When this solution is boiled, and the air has free access to it, it becomes indigo blue, or of a violet colour, which soon changes into brown. Concentrated nitric acid imparts a deep yellow colour to solid albumen, when the mixture is gently warmed. A solution of mercurous and mercuric nitrite and nitrate, which is made by dissolving one part of mercury in two parts of nitric acid, containing $4\frac{1}{2}$ molecules of water, and having a specific gravity of 1.41, imparts a saturated red colour to albumen in the solid or dissolved state, when the mixture is warmed to near boiling. The colour is not removed by the influence of the air, or by protracted boiling. This is a very delicate test for albumen. But it is not applicable to the urine, as four different precipitates are formed in it by this mercurial solution; one of the suboxyde with chlorine (calomel), one of the oxyde with urea, one of the albumen with the free nitric acid of the mercurial solution, and one with the colouring matter.

These precipitates obscure the red colour so much that frequently only a fawn or pale red colour remains, and that only when the coagulated albumen is transferred into a second quantity of mercurial solution.

A solution of iodine in hydriodic acid, or in iodide of potassium, imparts a brownish-yellow colour to albumen. When mixed with strong sulphuric acid and a solution of sugar, albumen yields a solution which is red at first, and afterwards assumes a violet colour.

When dry albumen is heated, it begins to melt at higher temperatures, and is decomposed, the mass swelling up, charring, and evolving an odour of burnt horn. When subject to destructive distillation, or allowed to putrify, albumen yields a variety of substances, among which formic, acetic, and other fatty acids, and benzoic acid, may be mentioned. Two crystallised substances of pathological significance are also obtained—leucine and tyrosine.

When a solution of albumen is precipitated with basic acetate of lead, the precipitate washed and suspended in water, and

carbonic acid is now passed through the mixture, the albumen is redissolved together with a little lead, which may be removed by sulphuretted hydrogen. The filtered solution, on evaporation at a temperature not exceeding 50° C., leaves solid soluble albumen, which is free from mineral constituents, and has an acid reaction when dissolved, as it contains some acetic acid.

When the temperature of a solution of albumen in water is raised to 60° C., it begins to get turbid in the upper strata, and on the temperature being raised to 75° C., the albumen coagulates in large flakes, which become more compact the higher the temperature is raised, or the longer the boiling is protracted. The more dilute a solution of albumen is, the higher is the temperature which it requires for coagulation. The free alkali, which is in combination with the albumen, requires to be neutralised before boiling by means of acetic acid, otherwise a part of the albumen will remain in solution, unaffected by any temperature. The addition of alkali to a solution of albumen may prevent its coagulation by heat.

During the coagulation of albumen from the egg, an evolution of sulphuretted hydrogen takes place. This is not the case when albumen from the blood is coagulated.

Solutions of albumen are precipitated by the addition of alcohol; strong spirit of wine transforms the albumen into the insoluble modification; dilute spirit of wine, however, precipitates it without change. Creosote, aniline, and other products of destructive distillation, coagulate albumen. Most mineral acids precipitate solutions of albumen. (The tribasic phosphoric acid is an exception to this rule.) The precipitate contains the acid employed in combination with coagulated albumen. This precipitate is soluble in a large excess of water, so that if we attempt to free it from the acid by washing with water it is almost entirely dissolved. Most organic acids—for example, acetic acid—do not precipitate albumen. A solution of albumen, however, slightly acidulated with acetic acid, and then diluted with a large bulk of water, or mixed with a concentrated solution of chloride of sodium, yields a precipitate of albumen. When gently warmed with an alkali, the soluble modification is transformed into the insoluble one, but remains dissolved in the alkali, from which it may be precipitated by acetic acid. Most salts of the oxydes of the heavy metals yield precipitates with solutions of albumen. The precipitation by corrosive sublimate may be mentioned as useful; when sublimate does not produce any precipitate in urine, in which we have to determine urea by means of the mercurial solution, we may be sure that no albumen is present likely to interfere with the correctness of the analysis.

A solution of albumen causes a turning of the plane of polarisation towards the left.

dition of an acid. The precipitate is changed in some degree, having lost part of its sulphur, which is sometimes evolved in the form of sulphuretted hydrogen. The insoluble modification is also soluble in concentrated acetic acid and common phosphoric acid; and in these solutions a precipitate is produced by ferrocyanide and ferricyanide of potassium. It is soluble in *very dilute* mineral acids, or at least is transformed into a jelly-like mass; the addition of a larger amount of acid to these solutions produces a precipitate. Concentrated hydrochloric acid, or sulphuric acid somewhat dilute, or a mixture of concentrated hydrochloric acid and some sulphuric acid, dissolve the insoluble modification of albumen formed by the aid of heat, and decomposes it. When this solution is boiled, and the air has free access to it, it becomes indigo blue, or of a violet colour, which soon changes into brown. Concentrated nitric acid imparts a deep yellow colour to solid albumen, when the mixture is gently warmed. A solution of mercurous and mercuric nitrite and nitrate, which is made by dissolving one part of mercury in two parts of nitric acid, containing $4\frac{1}{2}$ molecules of water, and having a specific gravity of 1.41, imparts a saturated red colour to albumen in the solid or dissolved state, when the mixture is warmed to near boiling. The colour is not removed by the influence of the air, or by protracted boiling. This is a very delicate test for albumen. But it is not applicable to the urine, as four different precipitates are formed in it by this mercurial solution; one of the suboxyde with chlorine (calomel), one of the oxyde with urea, one of the albumen with the free nitric acid of the mercurial solution, and one with the colouring matter.

These precipitates obscure the red colour so much that frequently only a fawn or pale red colour remains, and that only when the coagulated albumen is transferred into a second quantity of mercurial solution.

A solution of iodine in hydriodic acid, or in iodide of potassium, imparts a brownish-yellow colour to albumen. When mixed with strong sulphuric acid and a solution of sugar, albumen yields a solution which is red at first, and afterwards assumes a violet colour.

When dry albumen is heated, it begins to melt at higher temperatures, and is decomposed, the mass swelling up, charring, and evolving an odour of burnt horn. When subject to destructive distillation, or allowed to putrify, albumen yields a variety of substances, among which formic, acetic, and other fatty acids, and benzoic acid, may be mentioned. Two crystallised substances of pathological significance are also obtained—leucine and tyrosine.

When a solution of albumen is precipitated with basic acetate of lead, the precipitate washed and suspended in water, and

carbonic acid is now passed through the mixture, the albumen is redissolved together with a little lead, which may be removed by sulphuretted hydrogen. The filtered solution, on evaporation at a temperature not exceeding 50° C., leaves solid soluble albumen, which is free from mineral constituents, and has an acid reaction when dissolved, as it contains some acetic acid.

When the temperature of a solution of albumen in water is raised to 60° C., it begins to get turbid in the upper strata, and on the temperature being raised to 75° C., the albumen coagulates in large flakes, which become more compact the higher the temperature is raised, or the longer the boiling is protracted. The more dilute a solution of albumen is, the higher is the temperature which it requires for coagulation. The free alkali, which is in combination with the albumen, requires to be neutralised before boiling by means of acetic acid, otherwise a part of the albumen will remain in solution, unaffected by any temperature. The addition of alkali to a solution of albumen may prevent its coagulation by heat.

During the coagulation of albumen from the egg, an evolution of sulphuretted hydrogen takes place. This is not the case when albumen from the blood is coagulated.

Solutions of albumen are precipitated by the addition of alcohol; strong spirit of wine transforms the albumen into the insoluble modification; dilute spirit of wine, however, precipitates it without change. Creosote, aniline, and other products of destructive distillation, coagulate albumen. Most mineral acids precipitate solutions of albumen. (The tribasic phosphoric acid is an exception to this rule.) The precipitate contains the acid employed in combination with coagulated albumen. This precipitate is soluble in a large excess of water, so that if we attempt to free it from the acid by washing with water it is almost entirely dissolved. Most organic acids—for example, acetic acid—do not precipitate albumen. A solution of albumen, however, slightly acidulated with acetic acid, and then diluted with a large bulk of water, or mixed with a concentrated solution of chloride of sodium, yields a precipitate of albumen. When gently warmed with an alkali, the soluble modification is transformed into the insoluble one, but remains dissolved in the alkali, from which it may be precipitated by acetic acid. Most salts of the oxydes of the heavy metals yield precipitates with solutions of albumen. The precipitation by corrosive sublimate may be mentioned as useful; when sublimate does not produce any precipitate in urine, in which we have to determine urea by means of the mercurial solution, we may be sure that no albumen is present likely to interfere with the correctness of the analysis.

A solution of albumen causes a turning of the plane of polarisation towards the left.

The albumen of the blood is not precipitated by dilute sulphuric acid, yields no sulphuretted hydrogen on coagulation by heat, and contains less sulphur than the albumen of eggs. In all other respects both descriptions of albumen are pretty nearly identical.

The composition of albumen, as it occurs in the blood, is very similar to that of white of eggs.

	White of Eggs.	Albumen from Blood.
Carbon . . .	53.4	53.0
Hydrogen . . .	7.0	7.1
Nitrogen . . .	15.6	15.6
Oxygen . . .	22.4	23.1
Sulphur . . .	1.6	1.2
	<hr/> 100.0	<hr/> 100.0

Chemical Formula for Albumen.

According to the quantity of sulphur, white of eggs may contain more than 45, and albumen of blood more than 55 atoms of carbon. Notwithstanding this, the chemical characters of both descriptions of albumen are so much alike, that it is difficult to distinguish them by chemical tests. Lieberkühn attributed to both the formula $C_{86}H_{56}N_9O_{11}S$.

Diagnosis of Albumen in Urine.

Coagulation by Heat.—Care being taken that the urine have a slightly acid reaction, naturally or by the aid of some acid, as acetic acid, the albumen will coagulate at a temperature of from 60° to 100° C.

A precipitate of earthy phosphates cannot be mistaken for one of albumen, because it is soluble in a drop of almost any acid; because it never forms into flakes, as the albumen does, on protracted heating or ebullition; and because it redissolves on cooling, when formed under the influence of heat.

There is this caution to be observed—that an excess of any acid beyond the amount necessary for neutralising the free alkali of the albumen, will, on boiling, or without it in *very dilute solutions of albumen*, keep a certain proportion of it in solution, just as the precipitate of albumen and nitric acid dissolves in an excess of water. A slight turbidity from albumen, produced by boiling, may therefore disappear on the addition of a drop of acetic acid. This test seems to have been considered as the reaction of a modified albumen, but it is probably only the reaction of a very dilute albumen.

If the urine is alkaline, and the amount of albumen contained in it is small, it will not be coagulated by boiling. If the

amount of albumen be larger, a part corresponding to the amount of free alkali will be kept in solution.

Nitric Acid Test.—The addition of nitric acid to albuminous urine causes a white precipitate of a compound of nitric acid and albumen. This test, if used with certain precautions, is extremely delicate and handy. A small conical glass is filled to two-thirds of its height with urine, and some nitric acid is then allowed to flow along the wall of the glass towards the bottom, where it collects. It mixes with some urine, and forms a clear reddish, mostly dark stratum of fluid. If albumen is present, there will be, lying immediately on the acid, a turbid layer of a precipitate, so strongly distinguished both from the acid and the supernatant urine that it cannot easily be overlooked. When the amount of albumen is very small, the precipitate sometimes appears only after a few minutes, or becomes more distinct; but after standing longer, it diffuses in the fluid. But in most cases it appears readily and distinctly.

The addition of nitric acid to some descriptions of urine may cause a precipitate of uric acid. In the few cases in which I have met with this precipitate (cases of scarlet fever during the acme), it consisted of the hydrate of uric acid, as, on heating, the urine became speedily clear, and now was full of uric acid crystals. Under the microscope the precipitate was amorphous, transparent, in jelly-like masses, which when left to themselves quickly agglomerated into crystalline forms. This precipitate in every respect corresponds to that obtained by throwing a solution of urate of sodium into hydrochloric acid of the ordinary temperature. When the hydrochloric acid is previously made hot, the uric acid obtained is not jelly-like and hydrated, but crystallised, and with only two molecules of water. In correspondence with these facts, the urine gave no precipitate of fawn-coloured hydrate of uric acid with nitric acid, when it was heated before the addition of the acid, and the crystals formed quickly in a clear fluid. It is very improbable that urates should be precipitated from their solution in urine by nitric acid. But whether this precipitate be made up of urates, as Heller believes, or of uric acid as in the above-mentioned cases, not only the characters described by me, but also some described by Heller, readily distinguish it from albumen. For the precipitate resting on the clear layer of acid, when made up of uric acid or urates, diffuses in cloudy streaks through the entire stratum of supernatant urine, which the precipitate of albumen never does. And if in one and the same urine both albumen and uric acid are precipitated by nitric acid in the manner described, then the layers of the mixture are so arranged that upon the lowest clear layer of acid the layer of albumen follows; upon this there is another layer of clear urine; and uppermost floats a stratum of urine which is turbid from clouds of uric acid (or urates).

Chromic Acid Test.—When a small crystal of chromic acid is placed in a little normal urine, it dissolves without producing any precipitate. But when the urine is albuminous, the crystal produces a cloudy precipitate on its entering the fluid, and after its complete solution all albumen is precipitated in dark reddish-brown flakes.

Tannin is also a very good test for albumen in very small quantity. The watery solution of the purest crystallised tannin should be used, and be prepared fresh for each testing. Healthy urine does not react with tannin; albuminous urine gives a precipitate with it.

Senator (Virchow's "Archiv." 60 (1874) 476), has examined the albuminous substances in cases of acute and chronic nephritis, and come to the following results:—

In every urine which contains coagulable albumen, there is besides serum albumen, always (para)globuline; this latter is not proportionate in quantity to the total albumen, but varies according to the particular nature of the disease, most paraglobuline being apparently present in cases of amyloid degeneration of the kidney. Heynsius (Pflüger's "Archiv." 9, 526) has objected to these determinations, that the paraglobuline was precipitated from acid or alkaline urine, whereas all ought to have been made slightly alkaline before dilution with water and treatment with carbonic acid. The albuminous urine does not seem to contain alkali albuminate, or any albuminous body, which, after removal of paraglobuline, can be precipitated by acetic acid. Peptone is present in every albuminous urine, and, according to Gerhardt ("Deutsch. Archiv. Klin. Med." 5, 212), may be present in urine containing no coagulable albumen. Meissner and Subbotin ("Zeitschr. Ration. Med." 8, 282, and 33, 64) maintain that this alleged peptone is produced from the albumen of the urine. The rest of Senator's paper contains speculations as to the particular parts of the kidneys in which the different albuminous matters may be supposed to leave the blood and enter the excretion. For the disease expressed in the large, pale, fatty kidney, he believes this place to be the Malpighian glomerulus; in venous congestion from obstruction, however, the interstitial (looped) vessels; in other renal affections both co-operate.

Mode of Determining the Quantity of Albumen in Urine.

It is sometimes useful to know the quantities of albumen which a patient loses with his urine. The amount of lesion in the blood and kidneys may be approximately determined by this analysis, when all other symptoms are taken into consideration.

A measured quantity of filtered urine—50 c.c. when much, c.c. when little albumen is present—are most carefully

neutralised or slightly acidulated by means of dilute acetic acid. They are then put into a flask, placed in a water-bath, and the water is kept boiling for some minutes, until the thermometer, when placed in the flask, indicates that the temperature of the urine has risen to above 90° . When the urine has contained little albumen, the flask may be taken out of the water-bath, and placed over the free fire, and the urine heated to ebullition. The coagula are then collected on a filter of known weight, washed, and dried, first in the water-bath, afterwards in the air-bath, until no further loss of weight takes place. The amount of dry albumen thus found, when multiplied by the total amount of urine discharged in a given time, and compared with the known amount of albumen in the serum of the blood, gives us the key to the pathological deductions as to the nature and amount of the lesion, of which the exudation of albumen is a symptom.

Pathological Indications.

Leaving out of consideration all cases where the urine is albuminous from the presence of blood, pus, or, perhaps, though rarely, from an admixture of semen, *the presence of albumen in the urine indicates a pathological condition of the kidneys, of a temporary, chronic, or permanent nature.* The most elementary condition coming under this head is that of stasis of the blood in the capillary vessels, commonly called congestion. We know, from experiments on animals, that compression or ligature of the renal veins causes albumen to appear in the urine. We know that paralysis of the vascular and other nerves of the kidneys, which enter with the artery, by temporary constriction of the artery, or by complete division, a tube being inserted to keep up the circulation, has the same effect. We know, moreover, that a vitiated condition of the blood will make it unfit to pass the capillary vessels, and thus produce stasis in the kidneys. It is very probable that this is the mode of action of most diuretics, such as cantharides, turpentine, digitalis, and others, by which, indeed, albumen and blood may be made to appear in the urine; and this is also the most probable explanation of the way in which the specific poisons of scarlatina and allied diseases, and of typhus, gout, and rheumatism affect the kidneys. In all these diseases, or in certain stages thereof, albumen in the urine is of more or less common occurrence. We are acquainted with some other morbid conditions of the blood, artificial, or the consequences of disease, not being due to the introduction of a poison, which cause stasis in the kidneys and albumen in the urine. Thus the injection of large quantities of water into the blood, or a watery condition of the blood in the course of disease, with diminution of the albumen of the blood, known by the name of hydræmia and hypalbuminosis, will cause albumen to appear in

the urine. The injection of dissolved albumen into the blood has also sometimes had the same effect. But whether in these cases, as after injection of water, and the ligature of the abdominal aorta below the origin of the renal arteries, the appearance of albumen is due to increased pressure of the blood in the vascular system, or to the vitiated condition of the blood, or to both causes, remains to be decided.

Under all circumstances, however, the immediate cause of the exudation of albumen through the kidneys is increased pressure of the blood in the Malpighian bodies, whereby these bodies expand, and allow a certain amount of albumen to pass through their tissues. When the pressure becomes greater, rupture of the arteries is the necessary consequence.

The appearance of albumen in the urine is of very variable significance, according to the nature of the disease in the course of which it happens. It is most common in those diseases which find a local expression in the degenerations of the kidneys comprised under the name of Bright's disease, but which more lately have been appropriately classified according to their anatomical and symptomatic natures. The appearance of albumen, when due to any of these lesions, is always qualified by other symptoms, particularly the appearance of the fibrinous casts described in a former chapter.

In the course of some diseases albumen may appear in the urine for a single day, or for several, or for many days; and may disappear without leading to anatomical lesions of the kidneys. Thus in typhus albumen is not unfrequently found, particularly during the acme. I have observed albumen in the urine from acute cases of rheumatism. A girl, aged 15 years, was affected by violent rheumatic fever. On the worst day of the illness, when most joints of the limbs began to swell, she only discharged 60 c.c. of urine in twenty-four hours, which was dark red, and highly albuminous, without blood or casts. I have found albumen in several cases of acute and chronic rheumatism; in the latter particularly when an acute attack was threatening. In a case of hypertrophy of the heart I found albumen in scanty urine; and there being no evidence of organic lesion of the kidneys, the case was successfully treated by diuretics.

Albumen in the urine of patients labouring under an acute attack of gout is also common. Albumen in the urine of gouty and rheumatic patients seems to indicate that the disease, should it become of a chronic nature, has a tendency to produce those morbid conditions of the kidneys known as chronic desquamative disease, chronic purulent disease, wasting and fatty kidney, in the course of which the epithelium of the tubuli disappears, or degenerates fatty, or granular, as evidenced by the appearance of hyaloid, fatty or granular fibrinous casts.

According to Max Huppert (Virchow's "Archiv." 59, 367), every fully developed or abortive epileptic attack is immediately followed by a transitory appearance of albumen in the urine. The more pronounced the convulsion, the greater is the amount of albumen. The quantity of albumen also stands in a direct proportion to the duration of the disease, and the general frequency of the attacks.

CHAPTER XXXVIII.

CASTS OF URINIFEROUS TUBULES.

INTRODUCTION.

CASTS of the Bellinian tubules may be divided into several classes, according to the material of which they are made, and according to the condition of the tubes in which they are formed. We thus distinguish fibrinous casts, and casts the material of which is a fibrinoid substance insoluble in acetic acid. These are to be described in the present chapter, while blood casts will be described under the chapter discussing the anatomical elements of blood, and pus casts under the chapter relating to pus.

While the fibrine, or colloid matter, which in the course of certain diseases of the kidneys exudes through the walls of the Malpighian bodies, coagulates in the urinary tubules, it assumes the shape of these tubules and forms cast. We have to distinguish several descriptions of casts, according to the degree of the disorder which causes their formation, and according to the condition in which the fibrine or colloid matter finds the tubule on being effused into it. The simplest case is, that fibrine is effused into the tubule, there coagulates, separates from the epithelial walls by a slight contraction, and is expelled in the form of a homogeneous hyaloid cast of small diameter. But when the epithelium of the tubules manifests a tendency to separate from its basement membrane, and fibrine is exuded into the cavity of the tubules, the latter closely imbeds the epithelial cells into its substance, and, on subsequent contraction taking place, the cast of mixed fibrine and epithelium thus formed, is narrow enough to be removed through the channel of the tubule, and is found in the urine as a cast of the diameter of the urinary tubules, or of medium diameter. When the fibrine or colloid matter effused into the tubules finds an epithelium, which in consequence of former or chronic disease is imperfectly constituted, granular or fatty, a granular or fatty cast of medium diameter is formed. But when there is no epithelium left in the urinary tubule, when the basement membrane is for the greater part or wholly bare, then the plastic matter forms a homo-

geneous hyaloid cast of considerable diameter, containing little or no granular matter.

Casts of Small Diameter.

Intratubular Casts.—These transparent cylinders, by their small diameter and complete absence of epithelium, manifest themselves to be formed within the lumen of the epithelium of the tubuli, which does not desquamate during the formation of the casts. The diameter of the casts, little more or less than $\frac{1}{100}$ th of an inch, corresponds to the lumen of the canal, which is left in the axis of an ordinary tubule.

Their smooth and glistening surface is very characteristic. They may be so pale and destitute of shadows that they are entirely overlooked in a strong light. They become much more distinct when the light reflected through the microscope is moderated by means of the diaphragm.

Casts of Medium Diameter. $\frac{1}{100}$ th of an inch.

Epithelial Casts.—The fibrine which has been exuded by the Malpighian bodies has coagulated in the tubules, and entangled in its substance more or less of the epithelium of the tubules, and other substances accidentally present in their canals, such as blood corpuscles, and crystals of several substances, *e.g.*, oxalate of lime. Some free epithelium, in pieces or single cells, is always mixed with these casts, as the tendency of the epithelium to desquamate is evidently a feature not dependent upon the effusion of fibrine. It is, however, doubtful whether the desquamation of the epithelium in tubular masses does take place without the effusion of fibrine into its central canal. I have never seen casts consisting of the epithelium only; and in deposits where such casts, very similar to the tubular pieces of epithelium obtained by scraping from the cut surface of a healthy kidney, were present in abundance, I always discovered a large number of casts, consisting clearly of fibrine, with only a few epithelial cells embedded. By this observation I will by no means deny that casts consisting of the epithelium only may occur, as has been asserted by other observers.

Some authors have met with casts of medium diameter, containing well-formed dumb-bell crystals of oxalate of calcium, in the urine of patients suffering from cholera. In the same specimens also, octahedra of oxalate were present, but these latter were not entangled in the casts.

Granular Casts.—When the epithelium of the urinary tubule has been destroyed by chronic disease, it assumes the form of granular matter, and as such is entangled with the matter deposited in the tubes.

This deposit is always accompanied by granular matter not in the form of casts; so that there also the question arises, whether the degenerated epithelium is desquamated without the aid of cylinders. This can only be decided by long and careful observation. It cannot, however, be doubted that the effused matter materially assists in *quickly* removing desquamated epithelium, by the contraction which it undergoes soon after coagulation; a process by which the epithelium, when entangled, is completely separated from the liminary membrane, and the cast is enabled to pass the tubule, pressed onwards by the continued secretion and exudation from the Malpighian bodies, and perhaps by some contractile action of the matrix of the kidney.

Casts containing Fatty Matter.—These casts are of different diameters, but more generally of the medium diameter. They are formed in tubules, the epithelium of which is in a state of fatty degeneration. The casts may be hyaloid, with only a few oil-globules imbedded in their substance; or they may entangle some epithelial cells, filled with oil, showing that the fat is formed in the interior of the epithelial cells; or the fat may be present in large quantities. Free fatty cells are always present.

Casts of Considerable Diameter. $\frac{1}{8}$ th of an inch.

The diameter of these casts is nearly equal to that of the urinary tubules in which they have been formed. They are mostly perfectly transparent, hyaloid, of a glistening aspect, resembling in appearance the surface of wax as it cools after having been melted. They rarely include much granular matter in their substance, owing to the very cause of their large size being the total absence of epithelium from the liminary membrane in which they are moulded. When granular, however, in one part, and hyaloid in the other, they are, perhaps, not always of the largest size. Sometimes they may contain a few epithelial cells. Beale has observed and figured casts of considerable diameter, which were composed of a material in the interior differing from that which formed the rind of the casts. With these large casts the sediment mostly contains granular casts of medium diameter, and granular *débris* of degenerated epithelium of the tubules.

Pathological Indications of Casts of Uriniferous Tubules.

The presence in the urine of intratubular hyaloid casts indicates a chronic disease of the kidneys, termed *non-desquamative nephritis*, which is caused by a vitiated condition of the blood. As the expulsion from the organism of poisons causing this and similar diseases of the kidneys is mostly effected by a process, in which desquamation of the epithelium of the urinary tubules plays an important part, the fact of the epithelium not being cast off is an

unfavourable symptom, indicating the retention of the poison in the blood. These casts, therefore, where they form the entire bulk or greater part of a urinary deposit, must excite serious apprehension for the ultimate welfare of the patient.

The presence in the urine of epithelial casts is a symptom of a disease of the kidneys, caused by the entrance into the blood of a morbid substance, or a poison. Of poisons, cantharides and turpentine, of diseases, scarlatina and cholera are illustrations. The appearance of casts in the urine in such cases is not a very unfavourable symptom in itself, particularly when it is only of short duration. But when the epithelial casts become mixed with much blood or pus, or when the desquamation has a tendency to become of a chronic nature, from the causes continuing to influence it, then it becomes an unfavourable symptom in proportion to its duration.

The granular casts are indicative of chronic desquamative nephritis, and of degenerated condition of the epithelium of the urinary tubules. These casts and the casts containing fatty matter are frequently found in gouty subjects, and then give rise to an unfavourable prognosis. The prognosis is better in cases where the chronic desquamative nephritis is the sequel of the acute progress.

The casts containing fat or fatty epithelium are most frequently the sequel of non-desquamative disease of the kidneys, and indicate the presence of fatty degeneration of the kidneys in the so-called granular form.

The casts of considerable diameter may occur in all diseases of the kidneys, and may therefore accompany all other casts. The presence of these casts is under all circumstances evidence that there are Bellinian tubules totally deprived of their epithelium. Their importance as a pathological indication is therefore in a great measure dependent upon the nature of the affection, in the course of which they have been deposited.

The casts of the uriniferous tubules were subjected to micro-chemical examination by Rovida (Moleschott's "Unters. z. Naturlehre des Menschen," 11 (1872), 1). He found some soluble in acetic acid, some soluble in the urine at 62 to 80°, and others insoluble under these conditions. From this he concludes that they are not fibrine, but an albuminoid substance; in a subsequent communication ("Rendiconti d'Istit. Lombard. di Scienc. e Let." Feb 8, 1872) he doubts whether they might not be an acid albumen become solid. The statements are so diffuse and contradictory that it is difficult to extract anything definite from them for practical use.

CHAPTER XXXIX.

FAT AND OIL.

OCCURRENCE.

APART from any accidental admixture of these substances, which we caution the reader to guard against most scrupulously, they may occur in the urine as the products of diseased action in the body or urinary organs in *three different forms*.

(a.) As large and small oil-drops, floating on the surface of the urine. Such oil-drops, called oil because they remain fluid at the ordinary temperature of the air, and are glycerides of oleic acid, I found on the urine, taken from the bladder after death, of a woman who died of chronic purulent nephritis, with fatty degeneration of the left kidney. The oil-drops make a greasy spot appear on paper, and are easily soluble in ether.

(b.) As granular fat, most probably solid, or if not surrounded by an albuminous sphere, like the fat in an emulsion, identical with the granular fat enclosed in pus-cells, or epithelial cells of the urinary tubuli, being a product of their degeneration, called fatty from the presence of the fat. These cells and the granular fat are frequently embedded in casts of the urinary tubules.

(c.) As fat in very minute particles, appearing as mere points under the highest powers of the microscope, but rising to the surface of the urine, and collecting as a cream, as in some forms of chylous urine.

Chemical Characters.

These are very little known, but seem to be identical for the different descriptions enumerated. What we call fat and oil are most probably mixtures of different proportions of oleic and margaric glyceride. The fat, which is fluid at the ordinary temperature of the air, is in all probability the oleine.

Fat and oil are soluble in ether, and are deposited unchanged when the ether is evaporated; but when they are surrounded by cell-membranes, or albuminous husks, ether may fail to take up the whole of the fat. It then becomes necessary, not only to shake the urine with some ether, but to evaporate it to dryness, to boil the residue with some alcohol and acetic acid, to evaporate again, and then to extract the residue with ether. Even

this extract may be impure from some hippuric acid, which is to be removed by alcohol or water.

Kletzinsky found in the urine of persons labouring under Bright's disease the following quantities of fat in 1000 parts of urine :—0·24, 0·28, 0·35, 0·37, 0·38, 1·27 parts. The quantities of fatty matters found in various descriptions of chylous urine are stated under the chapter referring to that substance.

Pathological Indications.

Fat in coagulating or albuminous urine, when causing a milky appearance, is a feature of chylous urine. When occurring in drops, granules, and cells, it is an indication of fatty degeneration of the kidneys, particularly when the cells or granules occur in fibrinous casts of the tubuli.

Chemical Properties of Urostealith.

A fragment of a calculus placed on platinum foil, and heated, remains solid at first, then begins to fuse and swell up, and gives off a pungent odour, resembling that of shellack and benzoine. The substance next takes fire, and burns with a clear yellow flame; a voluminous charcoal ultimately remains, which, when thoroughly burned, leaves a small amount of ash, principally lime.

When boiled in water, urostealith becomes soft, but does not dissolve. It dissolves with difficulty in warm alcohol, easily in ether, and on evaporation is again obtained in an amorphous condition. If kept at a gentle heat for some time, it assumes a violet colour. It readily dissolves in a hot solution of caustic potassa forming a brown soap, which by treatment with an acid again separates into urostealith, and the salt of the acid. When heated with nitric acid, it yields a colourless solution, a slight quantity of gas being evolved. If this solution is evaporated, the residue, when treated with ammonia or potash, assumes a dark yellow colour.

It is not clear whether urostealith is a resin or a fat. Its elementary composition is entirely unknown.

A young man, æt. 24, was admitted into the General Hospital at Vienna, suffering from the symptoms which usually attend the presence of concretions in the urinary organs. There was pain in the region of the left kidney. On examination, a calculus was discovered to be present in the bladder. During several days he passed some concretions not larger than hemp-seeds; on a subsequent occasion, the concretions had a bloody surface; sometimes he passed small coagula of blood, at others crystals of triple phosphate. After the nature of the calculus had been made probable by the analysis of the concretions, which consisted of urostealith, the patient was treated with carbonate of sodium, when urostealith was found dissolved in the urine, and the phosphatic crusts of the calculus were passed by the urethra, in a broken-up condition.

CHAPTER XL.

MUCUS.

CHEMICAL CHARACTERS.

SOMETIMES it is possible to obtain pure mucus by filtration, free from epithelial elements; it is then a glass-like mass, almost invisible under the microscope. It does not coagulate by heat, but by the addition of alcohol. The precipitate is soluble in water. Acetic acid precipitates flaky masses, not soluble in an excess of acid. Mineral acids give precipitates, easily soluble in an excess of acid. I have frequently used hydrochloric acid for liquefying tough mucus, and making it fit to pass a filter. Gallic acid and basic acetate of lead precipitate the solutions of mucus; neutral acetate of lead, alum, and corrosive sublimate cause a turbidity.

The analysis of mucus yields the following result:—

Carbon	.	.	.	52.1
Hydrogen	.	.	.	7.0
Nitrogen	.	.	.	12.5
Oxygen	.	.	.	28.4
				<hr/>
				100.0

Physical Characters.

Mucus is tough and ropy; when urine in which it is contained is filtered, it remains on the filter, rarely passing through it. After drying, it forms a glistening membrane, like the mucus on the track of snails. Its diagnosis is always ensured by the number of epithelial cells embedded in its substance. But should there be any doubt whether there be any mucus in a microscopic specimen or not, the addition of a little dilute tincture of iodine will, by its precipitating and colouring effect upon the mucus, readily decide the question. The admixture of spermatie filaments, oxalate of calcium and triple phosphate crystals, phosphate of calcium, urate of ammonium, and tubular casts may be ascertained by the microscope and the respective tests.

Physiological Quantity.

This depends mainly on the nature of the urine passing through the bladder. Concentrated urine causes the exudation of more mucus from the bladder; dilute urine, when not altered otherwise, has no such effect. The largest quantity of mucus seems to be secreted during the night, perhaps owing to the concentrated nature of the night urine, or to the irritating influence of its longer retention.

The normal amount of mucus cannot be expressed in figures. It is best to accustom the eye to an estimate by frequent inspection in transmitted light of urine in glass vessels. Any excess at all important will then easily be perceived by the increased bulk of the cloud.

Excess of Mucus.

This may be caused by pathological conditions of the urine, particularly alkalinity from decomposed urea. A large quantity of free acid may have a similar effect. Thus, the strongly acid urine, which is voided by a person on the morning after the night on which larger doses of benzoic acid were taken, exhibits a mucous cloud double the size of that voided under ordinary circumstances.

The Pathological Indications

of an excess of mucus must depend upon the causes which produce it. As such, we may mention all conditions which are characterised by irritation of the urinary organs. Pathological conditions of the urine, the presence of foreign bodies and concretions in the bladder, idiopathic diseases of the bladder and its appendages—all these, and some others, may be indicated in part by an increased amount of mucus in the urine.

When the characteristic symptoms of other defined diseases are absent, and the secretions of an excess of mucus from the bladder is the only characteristic symptom, then it is termed blennorrhœa of the bladder, or cystorrhœa. The pathological conditions of the mucous membrane giving rise to this excessive secretion are probably not always alike; but they are mostly those of catarrh or chronic inflammation, and of venous engorgement, from enlarged vesical veins.

CHAPTER XLI.

PUS.

PHYSICAL APPEARANCE.

THE diagnosis of pus in urine rests upon the presence of pus-corpuscles, to be ascertained by the microscope, and upon the tests for albumen, as the presence of pus invariably makes the urine albuminous.

When pus is present in ordinary acid urine, even in small quantities, it always forms a deposit, the corpuscles subsiding towards the bottom of the vessel, while the albuminous liquor remains dissolved in the fluid. The deposit is easily diffused by agitation, but soon settles, first like a cloud in the lower strata of the urine, afterwards again to the bottom of the vessel. When pus is present in larger quantities it forms clouds in the lower strata of the urine.

Pus Corpuscles.

These bodies are nucleated cells, and do not differ in structure and reaction from the white cells of the blood or lymph corpuscles. In shape they are more or less globular, and hence are called pus globules. Their diameter varies between $\frac{1}{160}$ th and $\frac{1}{100}$ th of an inch. The nucleus, single or compound, is always present, and if not visible at once, may be made so by chemical agents. The outlines of many corpuscles are only faintly visible, better in a dull light than when illuminated too strongly. Many corpuscles have a granulated appearance, from matter deposited in the interior of the cell.

When brought into contact with water, the corpuscles swell up and become pale; and the outline is rendered indistinct. The granular appearance mostly disappears, but the nuclei and nucleoli become visible or more distinct. Acetic acid and dilute mineral acids cause the corpuscles to become pale and swell up, and the cell membrane frequently bursts under their influence, or disappears altogether. The nuclei are then set free, and exhibit their variable size, shape, and composition.

When pus globules are introduced into a concentrated solution of any neutral salt of the alkalies, such as sulphate of soda, the

endo- and exosmotic changes cause the globules to collapse; to assume irregular, star-like angular appearances; and to become granular, so as to appear as if covered with granules. The nucleus, under this treatment, mostly disappears in part or altogether. Similar changes are produced by these solutions on corpuscles which have been previously treated with acetic acid or water. When the nuclei have been made invisible by solutions of salt, the addition of acetic acid will not always afterwards make them visible again.

When treated with caustic alkalies, the pus globules are disintegrated, almost entirely destroyed, and on the addition of water are dissolved almost entirely, merely leaving a small gelatinous residue, in which some light and dark points are to be distinguished. If a deposit of pus from urine is agitated with an equal quantity of liquor potassæ, it forms a dense translucent, gelatinous, or mucous mass, often so solid that the tube in which the reaction has been performed can be inverted without any escaping. Similar changes are induced by the carbonate of ammonia, formed from urea during the decomposition of urine. The deposit of pus then becomes viscid, and so very much resembles mucus that it is not rarely mistaken for it. The globules disappear, being transformed into a gelatinous mass. The addition of acetic acid to this viscid urine will convert the mucous mass into a white granular deposit.

Urine containing pus is mostly slightly alkaline, and, as I have already stated, always albuminous. When the quantity of pus is very small, the albumen may escape detection, and the corpuscles being found as a sediment may induce the belief that pus might be present without albumen. The addition of a little chromic acid will always make the slightest traces of albumen visible.

Pathological Indications.

The presence of pus in the urine indicates suppuration in some part of the urinary organs or adjoining regions. But the diagnosis of the seat of that suppuration is in practice frequently surrounded with great difficulty. The principal pathological conditions which may give rise to the appearance of pus in the urine are the following:—

Purulent Disease of the Kidneys—Suppurative Nephritis.—This disease is sometimes the sequel of non-desquamative or desquamative nephritis, and then begins with the appearance of intra-epithelial, small, or large intra-membranous fibrinous casts, containing pus corpuscles. But when the limitant membrane of the tubuli becomes destroyed, the pus no longer assumes the shape of casts, but is simply mixed with the urine. In this manner one or both kidneys may be destroyed. When no history of the case is known, and no purulent casts are found,

these cases sometimes remain obscure for a period. If the discharge of pus in albuminous urine continues regularly for a length of time, even without local or general symptoms, almost certainly purulent nephritis exists.

Inflammation of the mucous membrane of the pelvis of the kidney, or pyelitis, in consequence of retention of urine from various causes, as taught by surgery, may cause pus to appear in the urine. The presence of concretions in the pelves and calyces may have the same effect. The relative symptoms ensure the appearance of pus to be assigned to its proper cause.

When the pus comes from the *ureters*, its formation is mostly accompanied by pain along the course of these organs.

In the bladder pus may form under various circumstances. Many diseases of the kidneys cause by the altered quality of the urine irritation of the bladder, and an increased discharge of mucus. There is no difference between mucus and pus corpuscles, if considered singly; it is therefore natural that the line where mucus ends and pus begins is not very distinct, at least to our present means of diagnosis. The distinction is of no great importance if the locality of the formation is known to be the bladder; which it is easy to know, as local symptoms are scarcely ever absent when the bladder is the seat of even superficial and secondary irritation. Catarrh of the bladder, in consequence of alkaline urine and its various causes as enumerated under that head, is one of the conditions to be mentioned. It often accompanies stone in the bladder, and is a frequent consequence of lithotripsy.

The pus may have its origin *in the urethra*, as in gonorrhoea and its frequent sequel, stricture. In these cases, particularly those of the former class, pus may always be obtained from the urethra without the admixture of urine.

In females the urine may have an admixture of pus from the *vagina* or the *uterus*.

Abscesses, which sometimes form in the pelvis, the sub-peritoneal cellular tissue, in consequence of puerperal fever, or other lesions, such as gun-shot wounds, may open into any part of the urinary passages. I have observed several cases where a pelvic abscess discharged itself entirely by way of the bladder.

When an abscess has become encased, without opening, the pus corpuscles undergo fatty degeneration. We then find the cells larger, transparent, and filled with numerous fat granules. The membranes are soon destroyed, and we see the few granular cells left over embedded into a mass of albumen and granular fat, from broken-up cells. When this description of pus, which has the colour, consistence, and odour of cream, is mixed with

the urine, it gives it a perfectly milky appearance. This admixture of pus, which may occur in the course of certain forms of purulent nephritis (as in the case described by me in the "Association Medical Journal" for April 26, 1856), must not be mistaken for chylous urine. Another mistake here to be referred to is that of Lehmann, who interprets all cases of chylous urine as purulent urine metamorphosed by alkalinity.

It is of importance to observe the particular shape of the pus corpuscles. Quite normal pus corpuscles of a perfectly circular outline, which, after treatment with acetic acid, exhibit the characteristic nucleus, composed mostly of two or three nucleoli, admit of the conclusion that the disease giving rise to their formation is of a mild form—a simple catarrh of the mucous membrane. But when the pus corpuscles are irregular in form and outline, and on treatment with acetic acid show an irregular nucleus, or an indistinct granular mass in their interior, or when such corpuscles are mixed with irregular debris, not particularly defined, the purulent destruction is evident, and the integrity of the organ where this formation takes place is in great danger, or lost altogether. Such pus would be the product of ulceration and tuberculosis.

CHAPTER XLII.

THE FERMENT OF UREA AND URINE.

HISTORY AND LITERATURE.

THE decomposition of urea, the general results of which we have already considered under the chapter referring to the reaction of urine, is caused by a ferment, regarding the nature of which there have lately taken place important discussions. Musculus ("Compt. Rend." 78, 1874) prepared a paper containing the ferment by filtering ammoniacal urine, washing the filter with water, drying and dyeing it with turmeric. When such paper, even after two years' keeping, is dipped into a solution of urea, and then exposed to the air, it begins to get brown after a few minutes; the colour becomes the darker the more urea there was in the solution. The change of colour is caused by the decomposition of urea to carbonate of ammonia which colours turmeric brown. Pasteur ("Memoir on Fermentation," 1862) had ascribed the fermentation of urine to the action of an organised ferment, having the shape of oblong grains attached to each other in couples, rarely in strings. This proposition was supported by Van Tieghem, who also rejected the hypothesis of the vesical mucus altered by air being the cause of the fermentation of urea. On the occasion of the discussion before the French Academy of a note by Gosselin and Robin concerning the dangers of alkaline urine and the means of providing against it (January 1874), Pasteur raised the question whether his ferment cells were not present in the bladder in cases of cystorrhœa with alkaline urine. He then, from observations, answered this question in the affirmative, as also did Gosselin and Robin.

After the publication of the researches of Musculus, Pasteur and Joubert set about to test these observations by repetition, and published their results in "Compt. Rend," 83 (1876), 5. They admit as completely exact the principal assertion of Musculus that there is a soluble ferment which is capable of transforming urea into ammoniac carbonate at the ordinary temperature. But they maintain with Van Tieghem, that every ammoniacal urine contains the microscopic organisms alluded to above, and they overcome the conflict between both admissions by the hypothesis of theirs, that the soluble ferment of Musculus

is produced by the little organised particles of Pasteur. They also state that the maximum of the soluble ferment produced coincides with the disappearance, or, as they term it, absence, of urea from urinary or other liquids, in which the organised ferment lives and multiplies.

Pasteur and Joubert claim that this is the first example of an organised autonomous ferment, which can be cultivated in liquids proper for its nutrition, producing during its development a soluble matter, which can itself produce the fermentation which is also the action of the organised being. They have, however, not stated how the action of the organised being can be studied free from the influence of interference of its alleged secretion or product, the soluble ferment, and it is therefore not certain whether the soluble ferment is not always and alone the cause of the hydration and decomposition of the urea.

Mode of Obtaining the Isolated Ferment.

The best material is the thick ropy ammoniacal urine of persons suffering from catarrh of the bladder, or cystorrhœa. Such urine cannot be filtered, as the ropy mucus contained in it soon stops up all the pores of the filter. But when absolute alcohol is added to it, the mucus is coagulated in the form of a tough white mass resembling fibrine. The precipitate is washed, dried, and powdered; it constitutes the ferment itself (*Musculus*, Pflüger's "Archiv." 12 (1876), 214). All filters which have served in this process, and to which a trace of the mucus adheres, may after having been dyed with turmeric, be used as test-paper for urea. Such paper is much stronger in its action than that obtained by simply filtering ordinary ammoniacal urine through it.

According to *Musculus* the fermentative action belongs to the amorphous mucus exclusively, and not to any ferment cells, such as those which are found in ordinary ammoniacal urine, and to the action of which the fermentation of urine is ordinarily attributed. For no such cells can be seen in the coagulated mucus, and, further, the ferment is soluble in water, and can be filtered from insoluble formed materials. When some of the ferment is placed in water it forms a turbid liquid, which on being placed upon a filter, passes at first turbid, but after some time clear. If to a little of the perfectly clear solution a small quantity of urea is added, the latter is changed very quickly into carbonate of ammonia.

Characters of the Ferment.

The clear solution obtained as just described contains only a very small amount of matter, but this has all the characters of mucus. Alcohol and acetic acid produce white precipitates in

the solution. Mercuric nitrate produces a precipitate, which on warming assumes a rose pink colour. Sodium chloride produces no change, and on boiling the fluid remains clear. The precipitate obtained by alcohol leaves on drying a brown amorphous glistening mass, which is again soluble in water, particularly with the aid of a little sodium chloride; in this state it still acts very energetically upon urea. 0.10 gm. dissolved in 50 c.c. of water at 34° to 40° changes 0.20 gm. of urea into carbonate of ammonia in less than an hour. The precipitate, however, which is obtained by acetic acid, has lost all power to act as urea ferment. Acetic acid destroys the ferment. The same effect is produced by a variety of other acids. If some ferment is introduced into water containing one part of HCl in thousand, and if ten minutes after the mixing the solution is neutralised with soda, a solution is obtained which has not the slightest effect upon urea. The ferment cannot have been destroyed by the newly-formed sodium chloride; for a solution of ferment in a solution of salt containing 20 per cent. acts like a solution of ferment in pure water. Even strong ferment paper, when immersed for ten minutes in water containing one part of HCl in thousand parts of mixture, and then washed with water containing alcohol, has entirely lost all fermentative properties. When immersed into one HCl in three thousand of water the ferment is only partially destroyed. Sulphuric, nitric, salicylic, and other acids act in a similar manner.

Heat destroys the ferment easily when it is moist, when dry already at 80°. Putrefaction also destroys it. Dilute alkalis arrest the action of, without destroying the ferment. Five per cent. of ammonia in any liquid stop the fermentation entirely. After neutralisation the ferment acts again.

Sodium chloride and other neutral alkali salts have no influence. Phenol, which destroys all organised ferments, has no influence whatever upon the urea ferment. Ferment paper, when impregnated with pure phenol, and then washed with alcohol, loses nothing of its activity. From this Musculus concludes that the ferment has nothing in common with the organised ferments, but resembles the soluble chemical ferments like diastase, salivary and pancreatic ferment.

The urea ferment seems to exercise its action on urea only; it is without effect upon uric and hippuric acid, kreatine, guanidine, dicyamidine, acetamide, and oxamide.

In the use of the ferment paper care has to be taken to avoid the presence in the solutions to be tested of calcium and magnesium salts, which effect double decomposition with ammoniac carbonate, and prevent the action of the latter upon the turmeric. Such salts may be removed by a little sodium carbonate, and the neutralised fluid may be then tested.

*Mode of Determining the Urea contained in Urine Quantitatively,
by means of the Intervention of the Ferment.*

10·0 c.c. of urine are treated with a little sodic carbonate, and then diluted with water until they measure 100· c.c. The solution is coloured by litmus, neutralised accurately by a dilute acid, mixed with 0·2 gram. of ferment powder, and warmed in a water-bath to between 35° and 40°. After an hour the urea is completely decomposed. By adding a solution of sulphuric acid of known strength, the quantity of the ammonia formed is determined, and from this the quantity of urea is calculated.

CHAPTER XLIII.

CANCER CELLS AND TUBERCULAR MATTER.

GENERAL DESCRIPTION.

THE mucous membrane of the urinary bladder is a favourite seat of a certain variety of medullary, and perhaps, in some instances, of epithelial cancer, called villous cancer by Rokitansky and subsequent anatomists, from its peculiar mode of growth in fine villous processes, which make it resemble the surface of a chorion. On the exterior of these villi, the elements of a medullary or melanotic cancer-juice adhere to it, consisting of nucleated cells of various shapes, which form a soft, or a more consistent deposit, and are often present in such quantity that they make up the greater part of the morbid mass in the bladder, into which then the vegetations seem to grow (Paget, "Surgical Pathol." 2, 513).

The cancerous matter appears in the urine in small lumps of cells. The latter may be large, enclosing secondary ones; or they may have thick walls, and become elongated into spindle-like bodies. The urine at the same time mostly contains blood and coagula. From these and the collateral symptoms, the diagnosis of this disease offers no difficulties.

When, however, the appearance of cancerous matter is due to cancer of the kidneys, it is frequently difficult to form a diagnosis.

Of tubercle, and consequent phthisis, of the kidneys, I saw a remarkable instance some years ago. It was there secondary to tuberculosis of the lungs, as it almost always is. In these cases the deposit consists of tubercular matter, irregular pus cells, fragments of cells and their nuclei, granular undefinable matter, and, more rarely, pieces of crystals of cholesterine.

The form of tuberculosis which most frequently gives rise to the appearance of tubercular matter in the urine is that which has its seat in the mucous membrane of the urinary organs generally, and hence proceeds to deeper structures. Tubercles of the kidneys, however, may primarily form in the cortical substance. The diagnosis between the two forms is not aided by the microscopic analysis of the urinary deposit.

CHAPTER XLIV.

CYSTICERCUS TÆNIE ECHINOCOCCUS.

OCCURRENCE AND SYMPTOMS.

THERE are several cases on record, in which cystic entozoa have been passed by the urethra. They are formed mostly, it appears, in the kidneys; more rarely grown in other parts of or adjacent to the urinary organs.

The cysts vary in size, from a pin's head to an inch in diameter (fig. 2). Their external surface has a semi-opaque granular, or smooth, enamel-like appearance. In shape they are more or less globular; sometimes flattened, at other times very irregularly formed; sometimes, particularly the large ones, shrunk; as if they had lost a portion of their fluid contents. They contain a fluid and some granular matter, in which latter fragments of echinococci and their characteristic hooklets may be mostly detected. The walls of the cysts are made up of several layers of structureless membrane; the innermost covered with a layer of granular matter; in the larger cysts with numerous prismatic, feather-shaped, and crossed crystals of triple phosphate.

The echinococci are found embedded in the granular matter of the inner surface, from which they are grown, and to which they sometimes are found yet to be attached by true pedicles. But as the cysts met with in the urine are usually very old, the echinococci are mostly detached from their basis, and partly or entirely disintegrated, so that in some cases neither echinococci nor hooklets can be detected by the most careful examination. Thus, in the case recorded by Sieveking ("The Lancet," Sept. 10, 1853), the echinococci had become disintegrated. In the case related by Simon ("The Lancet," Sept. 24, 1853), the cysts were passed entire, and contained swarms of perfect echinococci in different stages of growth, together with innumerable hooklets of parasites, dead and decomposed at some earlier period. In the case published by Barker ("Glasgow Med. Jour." 1856), the large cysts contained echinococci, the small cysts mostly contained none.

The echinococci are mostly retracted, more rarely stretched out at full length.

The symptoms incidental to the discharge of these cysts have been closely described by all observers. When the cysts proceeded from the kidneys, there was dull, aching pain, accompanied with sensation of fulness in the loins, obstruction in the ureter, with lancinating pain along its course, an immediate sense of relief incident upon the cyst finding its way into the vesical cavity; lastly, straining attempts to micturate, pain along the urethra, and particularly at its termination, with obstruction to the flow of urine, until the emission of the cyst made a sudden end to the distressing symptoms.

In the case communicated to Barker by J. J. Evans, the urine was opaque, and contained flakes of membrane, fragments of cysts. Such membranes were also passed in Sieveking's case.

The number of cysts thus passed by one patient, at various periods, stretching over many years (eight in the case of Evans), may be extraordinary, exceeding hundreds at a time, and thousands in the aggregate of all discharges.

There can be no difficulty in the diagnosis of these parasites; for, even if the echinococci themselves should not be found in the cyst, yet the peculiarity of the latter, in being composed of structureless layers of a hyaline or opaque substance, the produce of the parasite, will distinguish it from all membranous matters that may by any chance pass by the urethra.

For details of cases the reader may consult the "Med. Times and Gazette" for Feb. 17, 1855, where ten cases are given.

Development and Propagation of the Tænia and Cysticercus.

The cysticercus lives in cattle and man; it is there developed from eggs only which proceed from the ripe tænia echinococcus inhabiting the intestine of dogs. The cycle of life of this animal is therefore completed only by the successive infections of three animals. A dog harbours a tænia, and this parts with its last joint (proglottis), containing ripe eggs, or departs in person from the intestine. The proglottis (or tænia) may fall to the ground entire with all the eggs in it, or the eggs may be laid by the proglottis already in the intestinal canal, and leave it in separate clusters mixed with the fæces. These eggs are now eaten by cattle or man with their respective raw or uncooked, or accidentally admixed with cooked food.

Arrived in the intestine, they are developed into embryos, which penetrate into the organs of the abdominal cavity and the chest, and are there developed into the cystic form of echinococci, membranous bladders containing a viscid fluid. These cysts occur singly, or in numbers, amounting sometimes, in cases which have survived the immigration of the parasites many years, to several thousands. The multiplication of cysts takes place by endogenesis in this manner, that a primary cyst pro-

duces in its interior one or more secondary cysts, which latter, in their turn, may produce tertiary cysts, and so on. The exact mode in which these cysts are found, and their relation to the heads forming in the interior is not yet determined. When the membranes of these cysts are examined particularly on sections under the microscope, they are seen to consist of several layers of varying thickness, the surface of the innermost one, that is to say, the free inner surface of the cyst being mostly covered with granules in the way represented in the engraving (fig. 3). A microscopic scrutiny of this internal surface soon shows the presence of certain layers of dark matter, matrices, from which proceed streaks of lines, imitating narrow but long folds, wrinkles, or rugæ. In these folds there probably run vessels serving for the circulation of nutritive and the removal of effete materials, and attached to their free surface by means of stems, resembling fruit growing on the branches of a tree, are seen the embryos of the future tæniæ, appearing either as granular buds with no organisation, or as pear-shaped bodies, with four suckers, but as yet no hooklets, ultimately the embryos appear as oval bodies on a stem, their surface covered with chalk corpuscles, and their interior occupied by an involutioned head with four suckers, a proboscis or rostellum and two rings of minute hooklets, these latter numbering between thirty and fifty (fig. 5). When these oval bodies are carefully pressed, the neck and head can be everted, and the animal then clearly shows its structure as the embryo of the tænia represented above (fig. 4). The vascular system consists of a ring round the rostellum, above the suckers, from which four longitudinal vessels proceed backwards, of these two and two unite just before the stem, and two main vessels, the future lateral canals of the tænia, and enter the stem and pass into the rugæ and diffused vascular system of the cyst. According to some observers the echinococci on the rugæ are always, at least during the early stages of their formation, enclosed in a separate small cyst or hatching capsule. This capsule I have never observed in human or animal cysts, but it is not therefore necessary to believe that it does not exist, as the writers who describe it also admit that it bursts spontaneously and disappears from



FIG. 1.—Tænia
Echinococcus
($\times 20$).

sight. On a number of echinococci embryos I have observed peculiar outgrowths in the shape of water-bladders. These

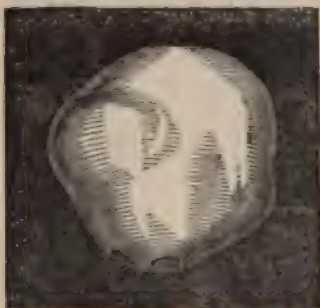


FIG. 2.—Echinococcus cyst from human kidney passed with the urine.

bladders were situated in various parts of the cysticerci, some showed only one, others two. If not produced by soaking and pressure, these bladders are probably pathological appendages of the animals. The echinococci of human beings most frequently go with them to their graves, or if they leave them by the ways of nature or the help of surgical operations during life, they are not permitted to continue their dangerous existence. But echinococci of cattle, particularly of sheep, are again set

free in the process of slaughtering; they are thrown on the

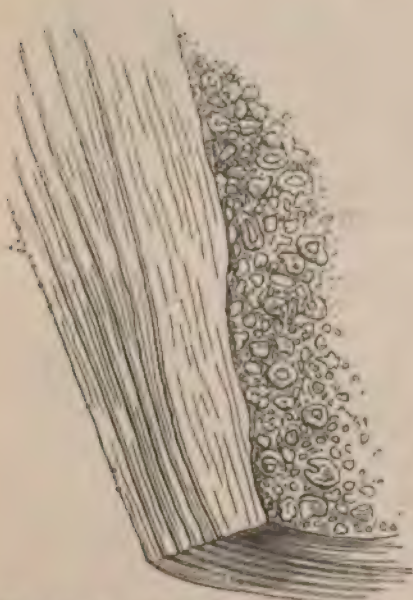


FIG. 3.—Sections and inner granular surface of cystic membrane of human Echinococcus magnified.



FIG. 4.—Echinococcus with head, rostellum, and suckers everted; the vessels in the interior and the chalk-corpuscles of the surface are also visible ($\times 40$).

ground and devoured by dogs, in them again to grow into ripe

tæniæ. While therefore man does not contribute to afford the opportunity for the multiplication and propagation of echinococci, his constant liability to the disease is kept up by the cycle of infection which subsists between dogs and sheep. The pig is also liable to be infected by echinococcus, but much more rarely than the sheep. Oxen and cows sometimes also have them, but still more rarely than pigs (*see* further details on occurrence in animals in my "Report on Parasitic Diseases of Quadrupeds used for Food," in Rep. Med. Off. Privy Council 1864-65, p. 334).



FIG. 5.—Matrix, rugæ, buds, and fully developed embryos, one with head and suckers protruded, from internal surface of Echinococcus of sheep.

Ingredients of the Fluid in Echinococcus Tumour.

Heintz had shown that the cysts of tumours contain sodic chloride, sugar, inosite, and sodic succinate; no albumen was found. Munk (Virchow's "Archiv." 63) analysed about 2 litres of such fluid. It had sp. gr. 1012, was of neutral reaction,

and left 1.574 per cent. of solid residue, of which 0.968 were ash, 0.606 organic matter. It did not coagulate on boiling, reduced alkaline copper solution, and its alcoholic extract after evaporation turned the plane of polarised light to the right. The sugar in the original fluid was 0.06 per cent. by the optical, 0.077 per cent. by the copper test. The liquid further contained a little urea and kreatine. Succinic acid could not certainly be proved to be present. Of the ash nearly two-thirds were sodic chloride.

CHAPTER XLV.

SPERMATIC FILAMENTS, OR SPERMATOOZA.

OCCURRENCE AND INDICATIONS.

THE occasional admixture of semen with the urine causes the characteristic filaments to appear in the deposits which may be examined for the purpose, or for some other object. The admixture with urine of semen in any quantity, so as to form a deposit for itself and make the urine albuminous, is not frequently if ever, met with in disease. In health this may occur under a variety of circumstances.

In the urine of males the presence of spermatic filaments in any quantity is necessarily the consequence of an emission of semen, which leaves some residue in the urethra, to be removed by the first urine passing the canal after the act. The emission itself, however, may be due to coition, or to spontaneous sexual excitement during sleep. Onanism may lead to the same result, and hence may sometimes be discovered thereby.

A not unfrequent cause of the escape of semen is extreme constipation; for after the passage of hard and scybalous fæces, an oozing of a whitish turbid fluid from the urethra, full of spermatozoa, is not uncommon.

Excluding the habitual emissions during sleep of persons affected with spinal disease, an ailment called spermatorrhœa has no existence. The few honest practitioners who believe in the existence of such a disease, are the credulous victims of onanists, who find it a strange satisfaction to seek relief and undergo all sorts of treatment for a supposed ailment, the continued cause of which they themselves knowingly are. I will exempt some cases, in which the victims of this vice think that medical treatment might heal them of their bodily passion, as they erroneously believe it to be. I make this statement in consequence of the confession of a young man, which he made to me in the hour of his death. This communication opened my eyes regarding these cases; and I have since that painful experience seen several cases, in which the complaints of spermatorrhœa and nightly involuntary emissions, on close examina-

tion, were found to be based upon no other grounds than continued spontaneous acts of the individual.

When found in the urine of women, where there is no possibility or probability of a fraudulent admixture, the spermatic filaments are evidence that coition has taken place. In medico-legal inquiries, the discovery of spermatozoa may sometimes lead to the disclosure of crime or vice.

Some microscopical inquirers state that the urine should be examined for spermatozoa as soon as possible after it has been passed, as they very rapidly become destroyed. Others, however, assert that urine, beyond making the filaments quiescent, exerts no further action upon them, as they may be detected, scarcely changed, even after it has become ammoniacal. The truth seems to be that the spermatic filaments are differently affected by different fluids; thus, in faintly alkaline or neutral urine they retain their motility much longer, but in acid or strongly ammoniacal urine they quickly become quiescent. In urine containing pus they retain their motility much longer, most probably because it is alkaline, as alkaline fluids, particularly caustic alkalies, are special excitants of the spermatic filaments, and may revive their peculiar motions under many circumstances.

When few spermatozoa are to be detected, the urine must be allowed to repose in a conical glass vessel; the deposit is then removed from the bottom by means of a caoutchouc pipette, brought into a cell, and examined under a power of from 300 to 400 diameters.

CHAPTER XLVI.

SARCINA VENTRICULI.

OCCURRENCE AND INDICATIONS.

THIS alga, also termed *Merismopædia punctata* (Meyen), which was discovered in vomited matters by Goodsir, belongs, according to Nägeli to the natural order of Palmellaceæ. It consists of particles in a peculiar cubic arrangement; there are generally not less than eight particles united within a structureless membrane, forming a cubic package, which looks like a bundle tightly bound by crossed strings. If these bodies multiply the increase is not cubic, but simply quadratic. In this manner four primary bundles of eight particles each are arranged into a square, presenting to the eye sixteen particles, but in reality being made up of thirty-two. Munk found cubes consisting of 512 particles.

The particles themselves are of a greenish or greenish-brown colour, of an irregular, rounded shape, and frequently present a dark point in their centre, from which Meyen derived the adjective given by him to the alga.

The sarcinæ occurring in human urine, and which undoubtedly may be developed in the bladder, have a more irregular arrangement than the algæ occurring in the stomach. When placed in creosote water, they show their peculiar movements for weeks afterwards.

The first observations of sarcina in urine were made by Heller. An exhaustive article on the subject was published by Welcker ("Zeitschr. f. Rat. Med." 5). Begbie ("Edinb. Med. Jour." 1856) and Munk ("Archiv. Pathol. Anat." 1861, p. 570) also published instructive articles.

When these algæ are discharged with the urine in great quantities, they form a greyish-white flocculent deposit.

Their occurrence in the urinary bladder is associated with catarrh and pain in the bladder, and in the region of the kidneys. They do not lose their vitality in either acid or ammoniacal urine. In the case described by Munk, that of a paraplegic patient confined continually to his bed, the algæ grew in great quantities during the summer months, and disappeared almost entirely during the winter months. In most cases dyspepsia was a collateral symptom.

CHAPTER XLVII.

COLOURING MATTERS OF BILE.

HISTORY AND LITERATURE.

FOR a complete account of the literature and history of inquiries the reader is referred to the researches of the author in the 10th Annual Report of the Med. Officer of the Privy Council for 1867, p. 240; further, to a paper by the author, published in the "Journ. of the Chem. Soc." May 1875; and to the author's "Open Letter to the Imperial Academy of Sciences at Vienna, containing an examination of the Researches on the Colouring Matter of Bile by Richard Maly of Graz," published in the "Chemical News" of April 13 and 21, 1876; in Liebig's "Annalen," 1876, and in Pflüger's "Archiv." 13 (1876).

Occurrence and Mode of Obtaining.

In human bile there are at least two colouring matters normally present, several others may occur abnormally. Of the former, one, bilirubine, is red or reddish-brown, and insoluble in alcohol, while another, bilifuscine, is dark brown and soluble in alcohol. Both are insoluble in dilute watery acids.

From human bile collected in the deadhouse these principles may be obtained in the following manner:—The bile is mixed with much alcohol, some ammonia and calcic chloride, and the deposit filtered off and exhausted with alcohol. The residue is treated with dilute hydrochloric acid. The earths being thus dissolved, the washed residue is extracted with alcohol, which dissolves bilifuscine. The insoluble part is now treated with chloroform, which dissolves bilirubine.

When bile is allowed to decompose in a closed vessel, it deposits both the forementioned colouring matters in the free state, owing to the formation of free acid; the deposit washed with a little acid, then with water, yields first bilifuscine to alcohol, then bilirubine to chloroform; a quantity of mucus remains insoluble.

From biliary calculi of man and animals these matters are obtained by exhausting the powdered calculi with water, alcohol, ether, and dilute hydrochloric acid in succession. Alcohol then

extracts bilifuscine, which is the prevailing coloured ingredient of human calculi, while chloroform extracts bilirubine, which prevails in the calculi of oxen, but in human calculi is present in small quantity only.

Bilirubine, $C_9H_8NO_2$.—It crystallises from its chloroform solution in reddish-brown rhombic prisms of very regular outlines, and greenish-blue lustre. When quickly deposited from its solution in chloroform, or caustic potash in alcohol, it appears as a red powder. It is insoluble in alcohol, very little soluble in ether; the best solvent is chloroform, of which 512 parts dissolve one part of bilirubine. It is easily soluble in caustic and carbonated alkalies; from its ammoniacal solutions it is precipitated by the salts of metals. These combinations are mostly either neutral or half-acid salts.

Neutral Silver Bilirubine, $C_9H_8AgNO_2 + H_2O$, is obtained as a red precipitate, when an excess of bilirubine is digested with ammonia, and the filtered solution precipitated with silver nitrate. It contains a molecule of water, which is not removed by drying in vacuo over sulphuric acid. In this respect the salt behaves similar to silver hippurate.

Neutral Bilirubine Baryum, $2(C_9H_8NO_2)Ba + 2H_2O$.—Dark brown powder, obtained by precipitating a solution of bilirubine in excess of ammonia with barytic chloride. It contains 27.56 per cent. Ba.

Half-Acid Bilirubine Baryum, $2(C_9H_8NO_2)Ba + C_9H_8NO_2 + 2H_2O$.—Dark brownish-red to dark brown powder, obtained by adding barytic chloride to a solution of bilirubine in ammonia digested with excess of bilirubine. Contains 20.75 Ba.

Neutral Bilirubine Calcium, $2(C_9H_8NO_2)Ca + 2H_2O$.—Produced like the analogous baryum salt, and like it containing two molecules of water. Contains 10.0 per cent. of Ca. This is the salt occurring in biliary calculi.

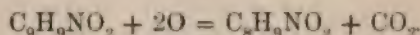
Half-Acid Bilirubine Calcium, $2(C_9H_8NO_2)Ca + C_9H_8NO_2 + 2H_2O$.—Produced like the analogous baryum salt. Contains 7.1 per cent. Ca.

There are similar salts of zinc, lead, and copper, and basic salts of silver and lead.

Dibromo-Bilirubine, $C_9H_7Br_2NO_2$.—When dry bilirubine is treated with bromine gas diluted with dry air as long as bromine is absorbed, it is transformed into a violet compound of the foregoing composition. The solutions in ether and alcohol present striking spectral phenomena, namely, a broad absorption band between the lines D and F.

Hydrobromo-Bilirubide Bilirubine, $C_9H_8BrNO + C_9H_8NO_2$.—When hydrobromic acid acts upon a hot solution of bilirubine in chloroform this body is formed, which easily passes into the hydrobromo-bilirubide, C_9H_8BrNO .

Biliverdine, $C_8H_9NO_2$.—When bilirubine is dissolved in caustic potash and exposed to the air it becomes gradually green. When the change is completed hydrochloric acid precipitates green flakes of biliverdine. This is easily soluble in alcohol with a saturated green colour. It arises from bilirubine by the addition of 2 atoms of oxygen and subsequent subtraction of a molecule of carbonic acid—



When bilirubine in alcohol is treated with nitric acid containing nitrous it becomes blue, violet, red, and ultimately yellow. The blue product can be isolated (cholocyanine), and has an absorption band in its spectrum between C and D. This reaction, known as Gmelin's test, can be instituted upon very dilute solutions or thin deposits of bilirubine, and is diagnostic. Bilirubine or biliverdine boiled with silver nitrate in excess of ammonia yield a green fluid, which on addition of an acid yields a dark violet precipitate. This gives to alcohol a violet-purple body. This test also is very diagnostic.

By treatment with fuming sulphuric acid, and subsequently water, bilirubine yields green cholothalline, $C_9H_{11}NO_3$, which has a peculiar spectrum of two bands, one in red, the other in green.

Bilifuscine occurs in bile and gallstones of man; it is brown, and soluble in alcohol and watery alkalies, without change of colour. Its composition is not ascertained, but it contains the same radical as bilirubine, and gives the nitroso-nitric acid test. It is precipitated by salts of lime and lead from alkaline solutions. It is probably present in icteric urine, together with matters derived from bilirubine, such as biliverdine, and biliprasine. This latter has a leek green colour, is soluble in alcohol, and in that solution becomes brown by acids, green by free ammonia.

Biliverdine, when treated with dry bromine vapour, is transformed into monobrominated biliverdine, a black powder of formula, $C_8H_8BrNO_2$. Both biliverdine and bilirubine when treated with sodium amalgam in soda solution, yield hydrogenated compounds of interesting spectral properties. Of abnormal colouring matters of bile occurring in small quantities in oxgallstones we know cholonematine, boviprasine, bovifuseopittine, museoprasine, ethochlorine and hyocoeeruleine.

Modes of Showing the Presence of Biliary Colouring Matter in Icteric Urine.

The appearance of biliary colouring matters in the urine in the course of disease is mostly recognised by a marked addition to or change in the colour of that liquid. It becomes deep yellowish-red, fiery red, reddish-brown or brown; on standing

exposed to the air it mostly becomes much darker, commonly of a greenish-brown appearance, particularly if it be of nearly neutral reaction.

A thin layer of the urine to be tested is spread over a white plate, and a drop of nitric acid containing some nitrous acid is placed in the centre of the circle. If biliary colouring matter is present, the margin of the drop of nitric acid will cause a blue colour to appear in the next circle of urine; the blue circle enlarges towards the circumference of the plate, and the circle next to the drop of nitric acid assumes a violet colour. The blue and violet circles expand, and an inner red circle appears. The test is now completed. The discoloration to yellow and brown which follow are neither constant nor characteristic.

Mode of Extracting the Biliary Colouring Matter from Urine.—It is stated that bilirubine can be extracted from acidified urine by shaking with chloroform. However, as such chloroform also extracts biliary acid and chromogen of urobilin, the residue which it leaves on evaporation must be subjected to a process of purification, for which the data are contained in the chapters on these substances. It is advisable to precipitate the colouring matter by basic lead acetate, and decompose the precipitate by acid, and after washing, extract it with chloroform to obtain bilirubine; or to precipitate the colouring matter by milk of lime, wash the precipitate, decompose it with acetic acid, and then extract with chloroform.

According to Prussak ("Centralbl. Med. Wissensch." 1867, p. 97), the urine of patients with strong fever and biliary obstruction does not contain bilirubine; and according to Huppert ("Zeitschr. Analyt. Chem." 6, 291 and 498), the biliary pigment contained in such urine is biliprasine. To prove the presence of this latter he recommends the following proceeding:—The urine is precipitated with milk of lime, the precipitate is collected, placed while in the moist state into a test-tube, and covered with absolute alcohol to half the capacity of the test-tube. Dilute sulphuric acid is added until the mixture, after shaking, has an acid reaction. The mixture is warmed, filtered, and the filtrate is heated to ebullition. The greenish-yellow, or yellowish-green liquid then changes its colour to a fine dark green. There must be excess of sulphuric acid present. When the fluid is boiled long it sometimes assumes a dark blue colour.

Pathological Considerations derived from Experiments upon Living Animals.—When Frerichs and Städeler had injected biliary acid solution into the blood of dogs, they obtained no biliary acids, but biliary colouring matter in the urine, and from this drew the conclusion that the biliary acids were changed in the blood into biliary pigments. Kühne, however, who had found the acids in the urine, sought the source of the bile-pig-

ment in these cases in the destruction of the blood corpuscles by the solutions of the salts of the bile acids. It was, however, soon discovered that in these experiments the bile acids were quite unnecessary, and that when a sufficient amount of water was injected into the blood, the supposed bile pigment would appear in the urine (Hermann, "Inaug. Diss." Berlin, 1859); and if a sufficient amount of blood corpuscles was destroyed by the water, the urine would become bloody with dissolved hematocrystalline. The experience was then used to prove that "biliary colouring matter," as the pigment in the urine was termed, was derived from the hematocrystalline, by its destruction in the blood directly, without the intervention of the liver. Naunyn (Du Bois-Reymond and Reichert's "Archiv. Physiol." 1869, p. 581) and Steiner (*ibid.* 1873, Heft. 2, pp. 160-194) were unable to confirm these allegations. On injecting from 10 to 20 c.c. of water into the common carotid of rabbits, they found neither blood nor biliary colouring matter in the urine. Only in two out of twenty-four experiments did Steiner find some biliary colouring matter in the urine after the injection, and these he explains as peculiar. The animals had eaten nothing for twenty-four hours after the experiment, and Naunyn had proved that in starving dogs, biliary matter appeared spontaneously in the urine. When Steiner injected from 30 to 50 c.c. water into the external jugular vein, he obtained, in twelve out of seventeen experiments, urine with dissolved blood; and when the blood had been removed by boiling, no biliary pigment was present in the urine, and none was in the precipitate. Thus the experiments of Kühne and Hermann were flatly contradicted.

Tarchanoff (Pflüger's "Archiv." 9, 53, and 9, 329) now came to the rescue of the hypothesis of the hematogenetic water-produced icterus. He maintained that Naunyn and Steiner had, in their tests of the urine, not sufficiently excluded the indogenous substance, "which in the presence of urea showed a bearing not unlike biliary pigment when treated with nitric acid." Considering that the results of Naunyn and Steiner had been mainly negative, the first thrust did not touch them.

Tarchanoff, however, having now perceived the weakness of the analytical proof of the presence of biliary pigment, bethought himself to improve the process for its identification. He would not boil the urine to remove the coagulable matters, as Kühne (Virchow's "Archiv." 14, 339) and Naunyn and Steiner had done (though Kühne's results had been positive, and the coagulable matters had not carried the biliary pigments down), but precipitated the urine with milk of lime, passed carbonic acid through the mixture, allowed to deposit by repose, filtered and washed the precipitate "moderately" with cold water. The precipitate was dissolved moist in acetic acid, and with this solution Gmelin's test was in-

stituted. He obtained a positive result. He also injected dissolved blood corpuscles into the vein of a dog with a biliary fistula, and obtained a curious result. The injection increased the secretion of bile; but its contents of matter soluble in alcohol were greatly diminished, while the colouring matter (estimated merely by the eye, and not in any way isolated or weighed or estimated objectively) rose to from four to about fifty times the quantity contained in the bile previously to the injection. When Tarchanoff injected bilirubin into the blood, he obtained a great increase in the colour of the bile, but no biliary pigment appeared in the urine. Feltz and Ritter (*Journ. d'Anat. et de Physiol. par Robin*, 7, 315) had injected 4 grm. of bilirubin in alkaline solution, and observed as consequences yellow colour of the conjunctiva and constipation, but no trace of biliary pigment appeared in the urine.

From these data Tarchanoff concluded that the ordinary belief that the biliary pigments were made in the liver was not supported by any direct evidence, but that it was more probable that they were made in the blood from hematocrystalline, and only excreted by the liver. He thus transferred the theatre of his experiments from the urinary to the biliary organs, and the chemical proof of the presence of biliary pigments in urine after injection into, or production in, the vascular system of dissolved blood corpuscles remained as unsatisfactory as it was before.

Tarchanoff's experiments and conclusions were called in question by Naunyn (Pflüger's "*Archiv.*") and to this Hoppe-Seyler (*ibid.* 10, 208) published a rejoinder in defence of his pupil, Tarchanoff. The discussion has not produced any new data.

As sporadic observations which must wait for an appreciation, we quote the statement of Orth (Virchow's "*Archiv.*" 63, 447), to the effect that he had found crystals of bilirubin (query, "uric acid") in the kidney-infarctus of newborn infants, and that of Vierordt ("*Die Quantitative Spectral Analyse*" and Pflüger's "*Archiv.*"), concerning a peculiar spectrum of an icteric urine.

*Pathological Indications of the Presence of Biliary Pigments
in Urine.*

After all the foregoing discussions, the pathological indications of the bilious urine do not seem altered from what they had been declared to be by clinical experience.

The occurrence in the urine of colouring matters being either identical with or derived from those of bile, indicates that the flow of bile from the liver into the intestinal canal is impeded or entirely suspended. The colouring matter of bile enters the blood by reabsorption, and hence passes into all the secretions and tissues; or the pigment, if it is really derived from hematocrystalline (which is yet very doubtful), not being excreted

from the blood by the liver, accumulates in the blood. Icterus or jaundice, as this state has been termed, is as easily diagnosed by the coloured tissues and colourless fæces, as from the brown urine, and its reaction with nitric acid.

There are, however, certain dissolutions of the blood consequent upon, or part of, the pathological process of pyæmia, others consequent now and then upon the bite of a serpent, or the terror it caused, and a third kind in the train of yellow fever—dissolutions which produce the green or yellow icteric colour of the skin and tissues, without being accompanied with retention of bile; as the frequent fluid evacuations contain abundance of green colouring matter, and the dark-red or brown urine does not show the biliary pigment test with nitric acid. The testing of the urine will distinguish these cases from true icterus.

CHAPTER XLVIII.

BILIARY ACIDS.

HISTORY AND LITERATURE.

GLYKOCHOLIC acid was discovered by Gmelin (Tiedemann und Gmelin, "Die Verdauung," 1824). The same observer also discovered taurine, a product of the decomposition of taurocholic acid, which latter acid was first isolated by Strecker ("Ann. Chem." 65, 7). The sodium salts of the mixed bile acids as they occur in bile were first obtained crystallised by Platner ("Die Galle," Wien, 1847, p. 126), and the colour test for bile acids was discovered by Pettenkofer ("Erdmann's Journ." 40, 129).

Occurrence.

The specific ingredients of bile are the products of the vital action of the liver, and have not as yet been found normally either in the blood or other parts of the body, the upper part of the intestine excepted. Nevertheless, they seem to be present in minute quantities in every healthy urine of persons of all ages and both sexes (Vogel of Dorpat, "Tagblatt. Naturforscher-Versamml." Leipzig, 1872, p. 75). In certain diseases, where the flow of the bile into the intestine is obstructed, biliary matters enter the circulation and appear in the urine in somewhat larger quantity—some in an altered, others in an unchanged, state. It seems that the first observation of the presence of biliary acids in urine was made by Pettenkofer upon a case of pneumonia. This discovery was all the happier, as the urine of pneumonic patients contains but very rarely abnormal quantities of biliary acids, and perhaps only in such cases where the right lung, its base, and the liver are simultaneously affected. The observation led also to the result, that biliary acids may be present in urine in which the biliary colouring matters are but feebly represented, while in urine from cases of strong jaundice, which contains much pigment, the biliary acids occur frequently in but very small quantity. The acids which occur in the urine are the same as those which are secreted in the bile, and do not seem to be transformed into cholic or any lower acid.

General Properties and Ingredients of Bile.

Human bile, as met with in the gall-bladder, is a yellow, greenish, or brown fluid, of a consistence imparted to it by the admixture of gelatinous mucus, of faintly alkaline reaction, and of bitter taste. It consists of nine-tenths of water, the amount of solids being only one-tenth. The main constituents are the salts, with alkalies, of two nitrogenised organic acids, of which one also contains sulphur—glykocholic and taurocholic acid. Second in order amongst the characteristic ingredients are the colouring matters, bilirubine and bilifuscine, also combined with alkalies. A third class of ingredients are the bodies of the lecithine class, phosphorised and nitrogenous, the latter property being due to the presence in them of a peculiar base which was first discovered in bile, choline; then there are fats, oleine, margarine, and stearine, and inorganic salts.

Crystallised Bile.

The bile is evaporated to dryness, and then extracted with alcohol. The alcoholic solution is decolorised by animal charcoal and distilled to dryness. The purified bile (1 part) is now dissolved in absolute alcohol (4 parts) with the aid of a higher temperature; and the solution, while yet warm, is mixed with small quantities of ether while being constantly agitated, until a coloured viscid matter begins to be deposited in considerable quantity. The bottle in which this operation has been carried on is now closed, and allowed to repose during several hours. After this interval the bottle contains a dense, dark, adhesive deposit, and a clear colourless liquid above it. The latter is decanted, put in a stoppered bottle, and exposed to the cold for some days, when the mixture of the alkali salts of the two acids crystallises. The isolated crystals are pressed between paper, dissolved in water, and acidified with sulphuric acid until a turbidity ensues; after twelve hours glykocholic acid is precipitated in a crystallised state, taurocholic acid remaining in solution.

Glykocholic Acid, $C_{26}H_{43}NO_6$

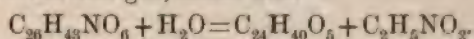
Glykocholic acid forms colourless, hair-fine needles, which are at first voluminous, and on drying shrink together, so as to form a paper-like mass, glistening like silk. It is very little soluble in cold water, more in boiling water; easily soluble in alcohol; little soluble in ether. It has a faintly acid reaction, and a sweet taste. It melts at a higher temperature and is decomposed, evolving at the same time a peculiar odour. When warmed with sulphuric acid and sugar, it yields a fluid of an intensely violet colour, which fluoresces green, and before the spectroscope exhibits characteristic absorption phenomena.

The salts of glykocholic acid with bases have a neutral reaction. The salts with alkalies and alkaline earths are easily soluble in water and alcohol, but insoluble in concentrated solutions of hydrated caustic alkalies or salts of alkalies. The salts with heavy metals are mostly insoluble in water. They do not crystallise from their solutions if they are evaporated; but the addition of ether will usually transform them into crystals.

Glykocholate of lead, $2(\text{C}_{26}\text{H}_{42}\text{NO}_6)\text{Pb}$, may be obtained when bile previously decolorised by animal charcoal is precipitated by plumbic acetate. The colourless salt may be decomposed by hydrothion, and glykocholic acid obtained by evaporation.

Glykocholic acid is soluble in concentrated sulphuric acid without discoloration, and on raising the temperature of the solution an amorphous precipitate forms, which is insoluble in water, and easily soluble in alcohol. This product, glykocholonic acid, contains a molecule of water less than glykocholic acid, and is $\text{C}_{26}\text{H}_{41}\text{NO}_5$. Its baryum salt is insoluble in water.

When glykocholic acid is boiled for some hours with dilute hydrochloric or sulphuric acid, it is split up into glykokoll, and an acid free from nitrogen, cholic acid—



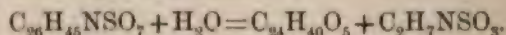
This decomposition, however, is rarely complete, as the resinous cholic acid encloses undecomposed glykocholic acid, which is then with difficulty influenced by the acid. On the other hand, a portion of the cholic acid is further decomposed, yielding dyslysine. This mixture of cholic and little glykocholic acid with dyslysine has such peculiar properties, remaining amorphous under circumstances where the separate acids, particularly the cholic acid, would crystallise, that it has hitherto been considered as a separate acid, to which the name choloidic has been given. This substance, however, always contains nitrogen, showing the presence of undecomposed glykocholic acid, yields cholic acid to boiling water (to be obtained in the crystallised state by the spontaneous evaporation of the solution), dissolves mostly in alcohol and alkalies, leaving some dyslysine undissolved, and on boiling with an alcoholic solution of potash yields large quantities of cholic acid, which now crystallises easily in the various forms and from the various solvents. Choloidic acid, therefore, has no existence, but what has been so termed is a mixture of glykocholic acid with two of the products of its decomposition. Glykocholic acid is more easily separated into glykokoll and cholic acid by the influence of caustic alkalies, or caustic baryta and long boiling.

Taurocholic Acid, $\text{C}_{26}\text{H}_{45}\text{NSO}_7$.

When glykocholic acid is precipitated by dilute sulphuric acid from the solution of crystallised bile, taurocholic acid remains in

solution, together with potassic sulphate. When this solution is evaporated to dryness and extracted with alcohol, and the alcohol is again evaporated, pure taurocholic acid remains as an amorphous mass. It may be obtained from bile directly, by treating the crude liquid with neutral acetate of lead as long as a precipitate ensues. Glykocholic acid, bilirubine, lecithine, and mucus are thereby removed. To the filtrate a little basic acetate of lead is added, which removes the rest of any glykocholic and a little taurocholic acid. The filtrate is now precipitated by basic lead acetate and ammonia. The precipitate by decomposition with hydrothion yields taurocholic acid. It has an acid reaction, a bitter and sweet taste; when the solution is evaporated it decomposes, so that the residue becomes partly insoluble. It is less changeable when in combination with alkalies, and the solution of such salts may be evaporated at the boiling heat. The watery solution of these salts froth like soap water; metallic salts form no precipitates with them, the sole exception being basic acetate of lead, and even that does not precipitate the whole of the acid.

Under the influence of caustic alkalies or baryta taurocholic acid yields cholic acid and taurine—



Taurocholic acid, therefore, has a constitution analogous to that of glykocholic acid, the difference consisting in the replacement of glykokoll by taurine.

Taurine and Glykokoll may be obtained from bile by boiling it with caustic baryta in excess for at least twenty-four hours. The liquid on cooling deposits crystalline cholate, which is removed and decomposed by hydrochloric acid to yield the free cholic acid. The mother-liquors are treated with carbonic acid, and the deposited carbonate, together with a little more cholate, are removed. The concentrated mother-liquor, on addition of alcohol and standing, deposits taurine in large crystals, to be purified by boiling with animal charcoal and recrystallising from water. The alcoholic solution contains glykokoll, which will crystallise on concentration. The mother-liquor contains choline, which is precipitated from the alcoholic solution by platinic chloride.

Taurine and glykokoll are amido-acids. They and choline can be produced synthetically.

Cholic acid, $\text{C}_{24}\text{H}_{40}\text{O}_5$, produced as above described, may also be obtained from bile by putrefaction. It is said also to occur in the intestine, and in the urine in the cases to be stated. It is free from nitrogen, readily crystallisable from water, alcohol, or ether, and forms crystalline salts with alkalies and alkaline earths.

It crystallises from alcohol in octahedra and tetrahedra belonging to the quadratic system. The crystals contain five molecules

of water of crystallisation upon two molecules of acid, being $2(\text{C}_{24}\text{H}_{40}\text{O}_6) + 5(\text{H}_2\text{O})$. In air they lose water and become opaque; at 100° they lose the whole of the water and then suffer no change on heating to 170° . Heated to 200° cholic acid loses two molecules of water and becomes dyslysine, $\text{C}_{24}\text{H}_{36}\text{O}_3$. Cholic acid is easily soluble in boiling alcohol, less soluble in cold, requiring 21 times its weight of 70 per cent. strength; it is soluble in 27 parts of ether, nearly insoluble in water. The alcoholic solution mixed with water, until it assumes a milky turbidity, or the ethereal solution on spontaneous evaporation, deposit the acid in needles of the composition $\text{C}_{24}\text{H}_{40}\text{O}_5 + \text{H}_2\text{O}$, which do not effloresce in the air, lose half their water at 100° , the whole at 130° , and fuse with decomposition at 145° . The solution of cholic acid turns the plane of polarisation towards the right.

Cholate of ammonium is obtained in needles when ammonia gas is conducted into an alcoholic solution of the acid, and ether is then added; when it is exposed to the air, or its watery solution is boiled, ammonia escapes. Potassic cholate, $\text{C}_{24}\text{H}_{39}\text{KO}_5$, is produced by adding to the alcoholic solution of the acid potash to neutrality and then ether. It forms needles which fuse at or above 150° . Baryum cholate, $2(\text{C}_{24}\text{H}_{39}\text{O}_5)\text{Ba}$, is produced by dissolving the acid in baryta water, precipitating any excess of baryta by carbonic acid, and evaporating the filtrate; it is deposited in silky crusts which are soluble in 30 parts of cold, 23 parts of boiling water, more soluble in alcohol. Silver cholate is precipitated from hot water in a crystalline state, and easily soluble in alcohol.

On the Presence of Biliary Acids in Icteric Urine.

The pathological chemists of the early part of the present century, the most prominent amongst them Orfila, believed that they could isolate the so-called resinous bodies of the bile from icteric urine. Thénard, Chevreul, and Lecanu were yet of opinion that the bile acids could sometimes be found; but Lehmann, Gorup-Besanez, Scherer, Frerichs, and others declared that they at least had never been able to find them. In consequence of this diversity of opinion, pathologists came to look upon jaundice as a term which might comprise two different diseases—one produced by a disturbance of the function of the liver, particularly an obstruction to the flow of the bile already secreted; the other caused by an anomalous condition of the blood, and not accompanied with any disturbance of the liver.

Frerichs and Städeler now transferred the discussion upon the field of experimental physiology, by injecting biliary acids into the circulation of dogs, and observing that the urine of these animals thereupon became icteric, while not yielding any bile acids on analysis. From this they concluded that the bile acids

were in the blood transformed into bile pigment, and that to such latter the icteric colour of the urine was due (Frerichs, "Klinik der Leberkrankheiten," 1, p. 101). The views of Frerichs were controverted by Hoppe-Seyler (Virchow's "Archiv," 13, 101), who evaporated icteric urine to a low bulk or to dryness, boiled the residue with hydrochloric acid, extracted the product with water, dissolved the matter insoluble in water in alcohol, and termed this dissolved matter choloidinic acid. The same process was also used by Kühne (Virchow's "Archiv," 14, 310) in some researches on icterus. Kühne showed, as far as the foregoing test can prove anything, against Frerichs, that bile acids injected into the blood of dogs do actually reappear unchanged in the urine, but that in passing through the blood they dissolve a portion of the blood corpuscles, and that the products of the decomposition of this free hemato-crystalline, eventually hematine, colour the tissues and the urine much in the manner of hepatic jaundice. Leyden now formulated the clinical distinctions of the two kinds of icterus, to this effect that in hepatic jaundice the urine contained some biliary acids as well as pigments, but that in hematogenous icterus the pigments alone, and no bile acids, appeared in urine; the normal urine he believed, with previous observers, to be free from bile acids. In the last conclusion he was supported by Folwarezny ("Zeitschr. d. Ges. d. Wiener Aerzte," 1859), and to a certain extent by Neukomm (Reichert and Du Bois-Reymond's "Archiv. d. Physiol." and "Ann. Chem." 116, 30), who found, if any, no more than traces of bile acids. Hoppe-Seyler (Virchow's "Archiv." 24,) now repeated his process on 30 litres of icteric urine, and added to the process a purification of the residue from the last alcohol extract, solution in alcohol and precipitation by ether. To meet other objections, Hoppe-Seyler now termed the product from icteric urine cholonic acid, and obtained it from more than thirty cases of icterus, but without ever saying whether he had applied the same process to healthy urine. He reversed the statement of other pathological chemists by enunciating, that the more colouring matter of bile a urine contained the greater was also the quantity of biliary acids in it, although pigments and acids were allowed not to be present in the same proportion as in bile.

It is not necessary to describe the products any further, as we know that the choloidinic acid for which they were taken does not exist, and because neither the analyses of the free product, nor that of its baryum salt led to any definite conclusion in favour of cholonic acid. The process is not of the slightest value, since we know that normal urine residues on boiling with acids will yield products which will show all the properties of the products described by Hoppe-Seyler, and which can be

separated into the different substances described in the chapter on urochrome, as uropittine, urochrome, omicholine, and omicholic acid. Whatever the product may have been, it must have contained several of these bodies, and though what we know now regarding the presence of bile acids in normal urine establishes almost a presumption in favour of the product having contained some dyslysine, nevertheless this dyslysine must have been mixed with the products just named, and therefore inaccessible to recognition by either tests or analyses. Consequently, all allegations concerning the presence of biliary acids in icteric urine, based upon the supposed finding of choloidinic or cholonic acid occurring in literature previously to 1863, must be treated with distrust whenever the method by which the acids are stated to have been found was the one just alluded to, or is not specially described.

But in 1863 Hoppe-Seyler ("Centralbl. f. d. Med. Wissensch." Nr. 22) published a case in which he succeeded in finding unchanged biliary acids in icteric urine by the following process:—1900 c.c. of strongly icteric urine were precipitated with basic lead acetate and ammonia, the precipitate was exhausted with boiling alcohol, the solution concentrated, the dissolved lead salt was decomposed with sodic carbonate. The solution was again evaporated to dryness, the residue dissolved in absolute alcohol, the alcoholic solution distilled to dryness, the residue was dissolved in water, the solution again precipitated by basic lead acetate and ammonia, the lead salt was again extracted with hot alcohol, and the extract decomposed with sodic carbonate; the solution was now evaporated to dryness, the residue extracted with little absolute alcohol, and the filtered extract precipitated with ether. After twenty-four hours crystallised salts appeared in the liquid, resembling those obtained under the name of crystallised bile. When the liquid was decanted the crystals liquefied. On addition of a few drops of sulphuric acid, a fine white amorphous precipitate ensued, which after twenty-four hours consisted of drops and crystals. The precipitate dissolved with difficulty in cold, more easily in hot, water, and on cooling was deposited again in the form of little drops and thin, long needles. These gave again a soda salt, soluble in alcohol. The salt gave Pettenkofer's test, showed the presence of nitrogen by Lassaigne's test, and its solution in water gave, with barytic chloride, a slight flaky precipitate, which dissolved by heat, or in more water. Burned with nitre the salt gave no sulphuric acid.

The ether alcohol from the first crystals was evaporated and left a viscous mass, which was dissolved in little absolute alcohol and precipitated by ether. The precipitate gave Pettenkofer's reaction, and burned with nitre showed sulphuric acid. It is therefore proved by these reactions, as far as reactions without

quantitative analyses can prove such a case, that in this icteric urine there were contained glykocholic, cholic (by baryta precipitate), and taurocholic acid.

On the Presence of Bile Acids in Normal Human Urine.

While the discussion on the presence or absence from icteric urine of biliary acids was continued during half a century, and the most circuitous routes were taken to arrive at proofs for the one or the other view, no one ever inquired whether normal urine contained any bile acids until Naunyn and Neukomm instituted inquiries in this direction and came to a positive result. Dragendorff then made some inquiries on normal urine, in which he used the following proceeding:—Four to five ounces of urine are acidified with a few drops of hydrochloric acid, and shaken with one ounce of chloroform (or amyl alcohol, "Zeitschr. f. analyt. Chemie," 8, 102) during at least one hour. The chloroform, which is said to be brown and turbid from the precipitation of the colouring and extractive matters, is now mixed with from 6 to 8 c.c. absolute alcohol, whereupon the mixture becomes clear again. It is put upon a filter and now changes to a thick gelatine, which prevents filtration. But by stirring the gelatine near the paper with a glass rod, filtration of chloroform and alcohol are effected. The filtrate is now allowed to evaporate spontaneously on watch glasses. The residue has a bitter taste. If a trace of sugar powder is added to it, and then concentrated sulphuric acid, a violet colour is produced at the margin of the mixture, particularly round the sugar granules, which lasts for about 15 to 30 minutes, and then passes into brown. This Dragendorff considers to be a sufficient reaction to the presence of bile acid. But to meet the objections which he himself foresaw as to its sufficiency for constituting a final proof, he adopted the following process:—He evaporated normal urine, extracted it with alcohol, evaporated again, and extracted with absolute alcohol; evaporated again, dissolved in water, and precipitated with basic lead acetate not in excess. The lead compound of bile acids was extracted with boiling alcohol, this solution evaporated after addition of sodic carbonate, and the residue extracted by absolute alcohol. This solution contained yet small quantities of a resinous urinary ingredient, which on treatment with sulphuric acid assumed a brownish-red, sometimes a feeble blue or violet colour, and when warmed with the addition of a little sugar, a red to yellowish-brown tint. The lead process had therefore to be repeated upon it. The ultimate residue was now tested with Pettenkofer's reaction, and, when the purple-violet was obtained, passed as a biliary acid salt. Or the residue was dissolved in a little water, acidulated with sulphuric acid, and shaken with chloroform; the latter on

evaporation left the free biliary acid, to be tested by Pettenkofer's reaction and by elementary analysis.

Dragendorff examined a litre of urine from each of ten persons, whose ages varied between 8 and 55 years, by the method just related, and found biliary acids in each. It seems that glykocholic acid alone was found, and no taurocholic. He then operated upon 100 litres of urine, and obtained the glykocholic acid in a pure state. A part of the biliary acid, he says, even crystallised in microscopic crystals, and its elementary analysis agreed perfectly with theory. The quantity of glykocholic acid obtained from the 100 litres of urine was estimated to amount to 0.7 to 0.8 gm. This subject was further elaborated by Höne in an inaugural dissertation, published at Dorpat in 1873.

Biliary Acids in the Urine in Diseases other than Hepatic.

Dragendorff applied his method of extraction with chloroform to the urine of patients suffering from phthisis, pneumonia, anæmia, diseases of the heart, brain, and skin, and found the purple reaction in all extracts. The urine of patients suffering from chronic diseases of the skin, who were being treated with endermatic application of tar, yielded the reaction with particular distinctness. The urine in these cases was particularly dark, without showing any reaction for biliary pigment. In five cases of jaundice, a case of cancer of the liver, and another of cirrhosis, the reaction was the most developed.

The foregoing reactions only show that in the diseases quoted the biliary acids present in normal urine are not wanting. They seem also to indicate that in diseases with hepatic obstruction the quantity of biliary acid excreted is larger than in health, but that in acute and chronic diseases not accompanied with hepatic obstruction the amount of biliary acids in the urine is not particularly changed. All these speculations rest, however, upon the assumption that the matter isolated by Dragendorff, Vogel, and Höne was really glykocholic acid, which is not yet quite certain, seeing that these authors have not shown what becomes of the chromogen of urobiline (so called) which chloroform must have extracted with their alleged bile acid. The description of his ultimate product by Dragendorff is also by no means satisfactory, and the maximum quantity of 0.8 gm. of material was scarcely enough for final determination. He also seems to have omitted the ether precipitation of his product, which would have excluded many doubts. Nevertheless there is a *prima facie* case made out, which will require the greatest attention of physiologists and pathologists.

I must here remark, in conclusion, that the Pettenkofer test as applied to urinary products is extremely deceptive, inasmuch as the chromogens and urochrome also yield strong red and

purple colorations with sulphuric acid. Under all circumstances, therefore, the identity of the reaction should be supported by the observation of its spectrum, which shows a dark, broad band overlying the D line, and in more concentrated and purer solutions, and strong light, two further bands near b and F.

Some authors have described even more simple processes for the discovery of bile acids in urine, such as allowing some sulphuric acid to flow to the bottom of a test-tube containing the urine to be tested, and observing a red ring at the line of contact. Seeing that the same procedure has been used to show, as was believed, the presence of indican, it requires no refutation. The conclusion that any red reaction occurring under these circumstances is due to bile acids is a mere fallacy. The reaction is due to chromogens and urochrome. This remark applies more particularly to the modified Pettenkofer test by Strassburg (Pflüger's "Archiv." 4, 461).

In repeating the Dragendorff-Vogel-Hone experiments with chloroform, Kälz ("Allgem. Med. Centralzeitung," Nr. 57, 1875) obtained extracts which yielded the purple test with sulphuric acid alone, and without the aid of sugar, and which he therefore declares to be urinary pigment, a chromogen not evidently related to bile acids. He discussed the question whether there might be some biliary acids admixed, but on comparing the reaction by sulphuric acid alone with that by sulphuric acid and sugar, he could discover no difference. This shows clearly that the chloroform extraction and colour test is no proof of the presence of biliary acids, and contributes to weaken our faith in the rest of Dragendorff's teaching.

In the urine from a case of poisoning by phosphorus, which was strongly icteric, Hilger ("Archiv. Pharm." 206 (May 1875), 385) found crystallised biliary acids by precipitating 500 c.c. directly with basic lead acetate and ammonia, and then proceeding further as above described. Feltz and Ritter ("Compt. Rend." 81, 793) having examined the urine of animals poisoned in various ways with phosphorus, putrid matters, emetic tartar, arsenite of soda, and arsenious acids, and using Pettenkofer's test only, have come to conclusions the criticism of which is contained in the foregoing.

CHAPTER XLIX.

GRAPE SUGAR, $C_6H_{12}O_6$.

HISTORY AND LITERATURE.

GRAPE SUGAR was found by Lowitz (Crell's "Chem. Ann." 1 (1792), p. 218 and p. 345) and Proust (Journ. d. Phys. et de Chim." 63, 257; 69, 428; "Ann. Chim." 57, 131 and 225) to be distinct from cane sugar. Thénard and Dupuytren ("Ann. Chim." 44, 45) proved the sugar from the urine of diabetic patients to be identical with grape sugar.

Occurrence.

This substance forms a constituent of all sweet-tasting fruit, in which it is contained in various proportions. Raisins, figs, dates, and other dried fruit contain it crystalline, and in largest proportions. It is also contained in bees' honey, mixed with an uncrystallised sugar, termed glucose.

It is found in the human and animal organism after food containing sugar or starch has been taken; the contents of the upper part of the small intestine, the chyle, portal and venous blood, and the extract from the liver, give then unquestionable evidence of its presence. But it is more than doubtful whether the substance found in hens' eggs, in the urine of the fœtus of the cow and sheep, in the allantoic and amniotic fluid of cows, sheep, and swine, which reduces oxyde of copper in its alkaline solution, is really sugar, as allantoine, a substance found to be present in all the fluids just named, has been found to possess the same reaction as sugar.

In diabetes mellitus, sugar is found in all or most of the secretions, tissues, juices, and excretions of the body.

Grape sugar may be made artificially from cane sugar and starch, either through the influence of diastase, or by boiling with dilute acids. Many immediate principles of plants, such as amygdaline, salicine, phloridzine, rhodeoretinic acid, rhuberythric acid, arbutine, populine, quercitrine, esculine, caincic acid, chinovic acid, tannic acid, and several animal principles, such as the cerebrine bodies of the brain, cartilage, and the chitin of lower animals, are under the influence of synaptase, or of dilute

acids or alkalies, transformed into grape sugar and other compounds. These principles are comprised under the class of *glucosides*, or substances combined with sugar.

Grape sugar turns the plane of polarisation to the right, and is therefore also called dextrose; by this property it is most easily distinguished from the uncrystallisable sugar of acid fruit, and of honey, which turns the plane of polarisation towards the left, and is therefore termed levulose. In fruit these two kinds of sugar are mostly present, but in human urine the dextrose grape sugar alone occurs, without any admixture of levulose.

Mode of Obtaining.

Honey is treated with cold alcohol, which dissolves the uncrystallisable sugar or *levulose*, leaving the crystallised grape sugar behind. The residue is washed with alcohol, pressed, dissolved in water, treated with animal charcoal, and clarified with white of egg, evaporated, and allowed to crystallise. It may be recrystallised from boiling alcohol.

From raisins or dates (which latter, when good and large, I have found most advantageous) it may be obtained by extraction with boiling water; the extract, when evaporated, is, after crystallisation has taken place, treated in the same way as honey.

From diabetic urine grape sugar may be obtained by evaporating the urine in the water-bath to dryness, extracting the crystalline dark-coloured residue with cold spirit of wine, and purifying the residue by repeated recrystallisation from water, after treatment with albumen and animal charcoal, and at last by recrystallisation from boiling alcohol.

Physical and Chemical Properties.

From somewhat concentrated solutions grape sugar crystallises in semi-globular warts, or in masses like cauliflower. From the watery extract of dates, and from bulky solutions in alcohol, large, transparent crystals, with well-formed planes, and double refraction of light, are sometimes obtained.

It is less soluble in water than cane sugar, requiring $1\frac{1}{2}$ times its own weight of this solvent for solution at the ordinary temperature. In boiling water it is soluble in all proportions. It tastes less sweet than cane sugar, and $2\frac{1}{2}$ parts of the former are required to equally sweeten the same bulk of fluid as one part of the latter.

The crystals contain a molecule of water, being $C_6H_{12}O_6 + H_2O$, which they lose at 100° , fusing at the same time. At 140° another loss of three molecules of water and simultaneous doubling of the sugar molecule transforms grape sugar into caramel, $C_{12}H_{18}O_9$.

Grape sugar, like cane sugar, unites with bases, but is easily coloured brown and decomposed while thus uniting. The baryum compound of the formula $2(\text{C}_6\text{H}_{12}\text{O}_6)\text{Ba}$ is obtained in the form of a flaky white precipitate by mixing together solutions in dilute alcohol of grape sugar and of baryta. A basic combination with lead is obtained by precipitating a solution of sugar by lead acetate and ammonia, its formula is $2(\text{C}_6\text{H}_{11}\text{O}_6)\text{Pb} + 2\text{PbO}$.

A compound of grape sugar with sodic chloride of the formula $2(\text{C}_6\text{H}_{12}\text{O}_6)\text{NaCl} + \text{H}_2\text{O}$ (Calloud, "Journ. d. Pharm." 11, 562) forms in inspissated diabetic urine. It may also be obtained by slowly evaporating a solution of grape sugar, saturated with sodic chloride, and by mixing moderately concentrated solutions of one molecule of sodic chloride with two molecules of grape sugar and gently evaporating the mixture; it crystallises in hard, colourless, six-sided double pyramids; if an excess of sodic chloride has been taken, this crystallises first from the solution. As the solution has to stand a long time before the crystals are fully formed, some mycelia are generally found on its surface; to the fibres of these perfect crystals are often found suspended. The compound is so pure that it can be used for controlling the strength of Fehling's solution instead of pure grape sugar.

Grape sugar is not influenced by dilute acids, and not blackened by concentrated sulphuric acid. If grape sugar dried at a temperature of 100° is mixed with one and a half times its weight of concentrated sulphuric acid, it dissolves and forms with the acid a combination which is an acid itself, and has been called sulpho-saccharic acid. This may be dissolved in water, and freed from excess of uncombined sulphuric acid by carbonate of baryum. The addition of basic acetate of lead to the filtrate precipitates sulpho-saccharate of lead, which by decomposition with sulphuretted hydrogen yields sulpho-saccharic acid, a substance which easily undergoes decomposition.

Grape sugar combines with the oxydes of metals. The compounds are, however, very changeable. Thus grape sugar combines with hydrated oxyde of copper to form an insoluble compound. On adding to 10 c.c. of a 2 per cent. solution of grape sugar 2 to 3 c.c. of a solution of caustic soda of 1.32 sp. gr., diluting with water, and then adding cupric sulphate to the mixture while constantly stirring it until the liquid has only a feebly alkaline reaction, a bluish-green precipitate is obtained which contains all the sugar and all the copper oxyde added. It can be washed with water and decomposed by hydrothion. Trommer's test, therefore, as originally used, consisted of two phases, the first being formation of a compound of sugar with cupric oxyde hydrate, the second resolution of this

compound is caustic alkali and reduction of the copper by the sugar. In the presence of bases it is easily oxydised, absorbs oxygen from the air, and assumes a brown colour. Thus when a solution of grape sugar, diabetic urine for example, is heated with a solution of caustic potash, the mixture becomes brown at a temperature of from 60° to 70° , and a smell of burned sugar is being evolved. Two acids, *glucic* and *melassic*, are produced by this process.

When the oxydes of several metals (copper, mercury, silver, gold, or bismuth) in the form of salts are brought in contact with solutions of grape sugar in a higher temperature, a reduction of the oxyde to a lower oxyde or to metal takes place.

Two reduction tests in particular are of importance for the qualitative discovery and quantitative determination of diabetic sugar in urine, the tests with bismuth and with copper.

When diabetic urine, or any other solution of grape sugar, is mixed with an equal volume of a solution of carbonate of sodium (made of three parts of water and one part of crystallised carbonate of sodium) and a pinch of basic nitrate of bismuth is added and the mixture heated to ebullition, the bismuth becomes grey or blackish from the formation of suboxyde of, or metallic, bismuth. If the process be watched attentively, the yellow oxyde of bismuth is discovered as a transition stage. This test is very easy and delicate, and very true in its application to urine, as none of the ordinary normal or pathological constituents of that fluid have the same influence upon the bismuth salt.

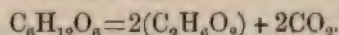
On adding to a solution of grape sugar some caustic potash, and afterwards, by drops, a dilute solution of sulphate of copper, a dark fluid is formed and, after a few seconds, a precipitate of hydrated suboxyde of copper ensues. On heating the mixture to ebullition, a discoloration of the fluid takes place, and all the copper is precipitated in the form of red suboxyde. A fluid containing one hundred-thousandth part of its own weight of grape sugar, when treated with caustic potash and a few drops of solution of sulphate of copper, yet yields a perceptible red precipitate on boiling. If a fluid contains one-millionth part of its own weight of grape sugar, the test is sufficiently delicate to give the fluid a reddish appearance, provided the fluid be in a thick layer (two or three inches in diameter), and properly illuminated.

The tests with caustic potash, bismuth, copper, and the analysis by optical means, furnish all evidence to be desired for the identification and determination of the quantity of grape sugar.

Grape sugar, when brought into contact with ferments, undergoes a series of decompositions, of which the following are the most important and best known :—

Vinous Fermentation.—A faintly acid solution of grape sugar,

when brought into contact with yeast, or putrefying matter, yields alcohol and carbonic acid—



This test was formerly used for determining the quantity of sugar in diabetic urine, &c. A known quantity of solution was mixed with yeast, and the carbonic acid, after passing through sulphuric acid for the purpose of retaining all the water, was allowed to escape. From the loss of weight in the apparatus, the amount of carbonic acid and its equivalent of sugar was determined by calculation. The experiment, however, requires too much time (three days) and too much attention, and the repeated use of the balance; and if applied to urine becomes unsafe, as other matters besides sugar are decomposed under the influence of ferment, so that it has been entirely abandoned.

Roberts has endeavoured to revive this method in another shape, for which he claims the twin advantages of ease and accuracy. He ferments diabetic urine with yeast, but instead of measuring or weighing the carbonic acid evolved, or the alcohol formed, he observes the specific gravity of the urine before and after fermentation, and from the difference calculates the quantity of sugar. In this process a diabetic urine, having from 1035 to 1050 sp. gr., may change its gr. to 1009, 1002, or even below 1000 if it contained much sugar. In practice the figure expressing the density lost is multiplied by the coefficient 0.23 (found empirically): the product expresses sugar in per cents. of urine ("Mem. Manchester Lit. and Philos. Soc." 1860; "Edinb. Monthl. Journ." October. 1861; see also Manassein, "Deutsch. Archiv. Klin. Med." 10, 73). The following test for sugar of Pratesi ("Imparziale," July 1, 1873) may perhaps be made useful for clinical purposes:—A solution is made of 60 parts of concentrated silicate of potash, two parts of potassic dichromate, and 2.5 parts caustic potash, all mixed in water. Of this mixture a small quantity is poured on the ends of small cuttings of block tin, and the drops are dried at a gentle heat; this is repeated on each cutting at least three times. This dry reagent slip will keep good for months. A drop of the urine to be tested for sugar is placed upon the slip, and slightly warmed. If sugar be present, the spot where the reagent was deposited will become green.

Lactic Acid Fermentation.—In an alkaline solution and in contact with putrefying matters, grape sugar is transformed into lactic acid, $\text{C}_3\text{H}_5\text{O}_3$, which possesses the same elementary composition as grape sugar, but only half its molecular weight.

Viscous Fermentation.—Under certain not well-defined conditions, sugar is transformed into mannite and a viscous gum-like

substance. This fermentation may be sometimes produced in diabetic urine by allowing it to stand in a stoppered bottle.

Quantitative Estimation of Grape Sugar by Volumetrical Analysis.

This analysis, based upon the copper reduction test of Trommer, received its present perfection at the hands of Fehling ("Journ. d. Pharm." 6, 301). By adding a solution of grape sugar of known strength to an alkaline solution of copper of known strength, until the latter is perfectly decomposed, it is found that one molecule of grape sugar decomposes five molecules of sulphate of copper, or 180 parts of grape sugar decompose 1246·8 parts of sulphate of copper, or 5 parts of grape sugar decompose 34·64 parts of sulphate of copper. If, therefore, 34·64 grm. of sulphate of copper are dissolved in one litre of fluid, 100 c.c. of the latter correspond to 0·5 grm. of grape sugar. The fluid is prepared in the following manner:—

Preparation of Test-Fluid.—34·64 grm. of pure air-dry sulphate of copper are dissolved in 160 grm. of distilled water. In the one-litre mixing-bottle 150 grm. of neutral tartrate of potash are dissolved in from 600 to 700 c.c. of solution of caustic soda of 1·12 specific gravity: to this the solution of copper is added gradually, and then the bottle is filled up to the litre mark with distilled water.

Application of the Fluid.—A known bulk (10 c.c.) of this fluid (of which 100 c.c., when completely reduced, indicate the oxydation of 0·5 grm. of grape sugar) is put into a capacious porcelain dish, diluted with a large quantity of water, say four times its bulk, and heated to nearly the boiling point. The urine, which has been diluted with ten or twenty times its volume of water, according to the quantity of sugar which may be estimated to be contained in it, and has been filled into the burette, is now allowed to flow into the boiling solution of copper. The suboxyde of copper is at once precipitated, and its red colour imparts to the blue fluid a greenish-brown colour, which gradually, under the cautious addition of more sugar solution, is transformed into a burning red. At the same time the blue colour of the mixture is fast disappearing, and when it has become quite colourless the reaction is complete. Towards the end of the reaction great care is required not to add an excess of the diabetic urine, as the analysis would thereby become useless. The addition of urine in drops may be continued as long as it produces a light yellow cloud on the surface of the fluid. This is newly-formed hydrate of the suboxyde, which becomes at once transformed into the anhydrous red variety. As soon as the urine on being dropped in ceases to produce a fresh cloud, it is necessary to remove the flame from underneath the dish, and to allow the precipitate to deposit. If the fluid appears quite colourless, the

reaction is complete. If, however, the slightest blue tinge remains visible on the white porcelain dish, then the addition of another drop of the urine, and another ebullition, is almost sure to remove it; and so on until the completion of the reaction is attained. The amount of urine which corresponds to the known amount of copper solution of known strength is now read off the scale on the burette, and from it the amount of sugar in the urine used, and that secreted within a certain period of time, is now ascertained by calculation. If therefore 10 c.c. of the copper solution have been taken, the amount of urine used for the reduction contains 0.05 grm. of grape sugar.

The copper solution becomes decomposed by keeping, a part of the tartaric acid being transformed into racemic acid, which also reduces the oxyde of copper on boiling. If therefore the graduated test-fluid has been kept for some time, it is necessary to ascertain whether it has formed a precipitate in the bottle, and whether it is precipitated by boiling. In the former case it may be cleared by filtration, and afterwards regraduated upon a solution of sugar of known strength. If, however, it forms a precipitate on boiling, it is spoiled, and must be thrown away.

Optical Saccharimetry.

An accurate method of ascertaining the presence and quantity of sugar in solutions is based upon the optical properties of these solutions. Cane sugar and grape sugar divert towards the right the plane of polarisation. If therefore a fluid contains either of these descriptions of sugar, and no other active substance, the quantity of sugar in solution may be ascertained by measuring the degree of diversion which the fluid exerts upon the plane of polarisation. For this experiment a polarimeter is employed. There are various forms of this instrument. I here describe those only which are either the most handy or the most accurate, and first, that of Biot and Soleil, as improved by Mitscherlich.

Before proceeding to determine the amount of sugar in a solution of grape sugar (urine), it is necessary to make sure that the zero point of the apparatus be accurately determined. This is the case when, after the empty tube has been put in its place, and the light of a lamp has been placed an inch or two behind the posterior aperture of the apparatus, and in the axis of the tube, the posterior aperture appears perfectly dark—almost black—to the eye looking in at the anterior aperture. If the index which moves upon the graduated circle surrounding the anterior aperture is now being moved from zero towards the right or left hand side, the posterior aperture becomes gradually lighted up, until at last it becomes quite a bright circle, the light being most intense when the hand shows 90° on the graduated disk, either on the right or left. On going back again from 90°

to zero, the observer will find that the posterior aperture, even though the hand be exactly at zero, is faintly lighted up at two opposite margins, and that the diameter of the circle, which runs parallel with the faintly illuminated margins, is the darkest part of the circle or spectrum, and appears intensely black. This blackest part must exactly divide the spectrum into two equal halves, when the hand indicates zero: the apparatus is then ready for use.

If the tube is now filled with a colourless solution of sugar (diabetic urine is mostly quite colourless, and scarcely ever requires treatment with animal charcoal, but mostly filtration), and put into its former place, the spectrum, which was black before, will now appear illuminated in colours, which, when the hand is again turned from zero to 90° , appear in the following succession: yellow, green, blue, violet, red.

The formerly darkest line of the spectrum corresponds now to the line where the violet and blue colour change into each other, and this line is the zero point for quantitative determinations.

A little practice will soon accustom the eye to determine the point at which the spectrum is divided into two equal halves, of which the one is violet, the other blue, and each colour of about the same intensity.

In case it is necessary to turn the hand towards the right in order to obtain the above succession of colours, then the fluid is said to divert towards the right the plane of polarisation, or turn towards the right a pencil of polarised light; this effect is obtained by a solution of grape sugar, dextrose, or saccharine urine. In the contrary case, the plane of polarisation is said to be diverted towards the left; this effect is obtained with fruit sugar or levulose. The angle in which the hand has to be turned is proportionate to the concentration of the fluid and the length of the column through which the polarised light has to pass, viz., to the length of the tube in the apparatus. In Mitscherlich's apparatus the length of the tube is 200 millimètres.

Supposing a fluid of a certain concentration to be put into the tube, the hand standing at zero, and that in order to see one-half of the spectrum violet, the other red, a rotation of the hand of 40° be required, then the same fluid in a tube of half the length would turn the hand only to 20° .

On the other hand, if 15 grm. of sugar be dissolved in any certain quantity of water, and the solution be poured into the tube so as to fill it; and if then the hand be turned until the colours of the zero point appear—for which we will assume a rotation of 15° to be requisite—then a solution of 30 grm. of sugar in the same quantity of water as the 15 grm. were dissolved in, when filled into the tube, will require exactly double the rotation, namely 30° , for the test colours to appear.

It has been found by accurate experiments that 15 grm. of pure and dry grape sugar, when dissolved in so much water that the solution amounts to exactly 50 c.c., will make a fluid a column of which, 200 millimètres in length, will turn the plane of polarisation 40° towards the right.

Upon the basis of this experiment it is easy to determine the amount of sugar in any fluid. Supposing the above tube, full of bright, faintly yellow diabetic urine, requires a movement of the hand from 0 to 30, then

$$40 : 30 = 15 : x; x = 11.25$$

which, in words, means that with a rotation of 30° there are 11.25 grm. of sugar contained in 50 c.c. of this diabetic urine. Another equation shows the amount of sugar contained in the urine passed during a certain length of time.

Jellett's Polarimeter.—The most accurate polarimeter extant is the one which was invented some years ago by Mr J. H. Jellett, Professor of Natural Philosophy in the University of Dublin ("Proceedings of the Royal Irish Academy," vol. 7). As the polariscopes ordinarily in use do not allow an observation of rotation in liquids containing less than 0.2 per cent. of sugar, but as Jellett's polariscope enables rotation to be determined with liquids containing as little as 0.01 per cent. of sugar, the instrument can truly be said to be twenty times more accurate than those ordinarily in use.

In determining the plane of polarisation of a ray by means of the ordinary Nicol's prism, the observer is required to arrest the rotation of the prism at the point at which the intensity of the transmitted light is at a minimum. But it is difficult to do this with very great accuracy, inasmuch as the observer is obliged to compare a shade of colour not with any other shade which is before his eyes at the same instant, but with his recollection of a shade observed at the previous instant. To insure any tolerable degree of accuracy the observation must be made very rapidly, so that the eye may receive the new impression while the former one is still quite fresh in the memory. The difficulty of doing this with accuracy in any case is obvious, but it is most felt in experimenting on light reflected or transmitted by fluids. For here it is impossible to touch the instrument without producing a tremulous motion in the fluid, and therefore in the image reflected or transmitted; and this motion while it lasts renders accurate observation very difficult. But if the rotation of the analysing prism be stopped for a sufficient length of time to allow this motion to cease, the recollection of the previously existing tint will no longer be so fresh as to allow the comparison to be made with any very great exactness. The difficulty will be

increased, as is easily seen, when there is any amount of elliptic polarisation in the light which is to be examined.

The remedy for this difficulty Jellett sought in the construction of an analyser in which the tints compared should be *simultaneous*, not consecutive. The double quartz plate of Arago was an attempt to realise this conception. It has, however, no similarity in principle to, and does not approach in accuracy, the following instrument devised for this purpose:—

A rhombic prism of Iceland spar, whose longitudinal edges

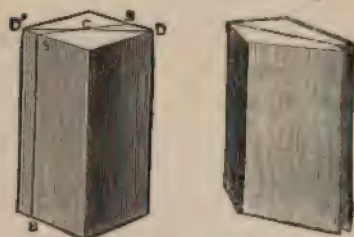


FIG. 1.—Prism (1). FIG. 2.—Prism (2).

should have a length of about two inches, or a little more, is cut by two planes perpendicular to those edges, so as to form a right prism, as in the engraving (fig. 1.)

This prism is next divided by a plane $S S' B$, parallel to the edges and making a small angle with the longer diagonal of the terminal face $D' D$; one of the two parts into which the prism is thus divided is then reversed,

so as to place the base uppermost; the two parts are cemented together, as in fig. 2, with the surfaces of section in contact, and the ends of the prism thus formed are then ground and polished.

Now it is evident from the construction of the prism, that if two rays of light parallel to the axis be made to traverse the two

parts of the prism respectively, the lines of separation of the ordinary and extraordinary images in these two parts will be $C A$, $C A'$ (fig. 3); and as the angle between the plane of section and the longer diagonal is small, the angle $A C A'$ is nearly 180° . Hence the extraordinary refractions in the two parts are in nearly opposite directions; and if the end at which the light is admitted be so chosen that these refractions shall be *from* the plane of section, the separation of the images will be nearly doubled.



FIG. 3.—Images in Jellett's Polariscopes.

to be equally divided by the plane of section, the emergent beam will consist of three separate parts, viz., (1) a circular beam, $O C O'$ (fig. 3), formed by the union of the two ordinary beams; (2) two semicircular extraordinary beams, $E E'$. If, then, the size

Now suppose a circular beam of plane polarised light to traverse the prism in a direction parallel to the sides, and so as

of the incident beam be suitably determined, these latter may be completely separated from the ordinary beam, so as to admit of their being stopped by a diaphragm which allows the ordinary beam to pass; the instrument will then transmit a single beam of plane polarised light.

The planes of polarisation of the two parts into which the beam is divided by the plane of section are inclined to each other at an angle somewhat less than double the angle $D C S$ (fig. 1). Suppose, then, that the plane of the paper being perpendicular to the beam, the traces of these planes of polarisation are represented by $A B$, $A' B'$ (fig. 4), and let $C P$ and $C P'$ be perpendicular to these lines respectively. Let $C p$ be the plane of polarisation of the ray to be examined.

Then so long as there is any difference between the angles $P C p$, $P' C p$, the intensities of the two parts of the beam will be different, and conversely, if these intensities be equal, it is evident that the required plane of polarisation will bisect the angle $P C P'$. The prism must therefore be turned on its axis until the equality of tints be established, and when this is done, the position $C p$ of the plane of polarisation is known. It is not, however, necessary to determine the position of the planes $P C$, $P' C$. The observer commences by transmitting a beam whose plane of polarisation is known, and turning the analysing prism until the tints become equal. The beam whose plane is required is then introduced, and when the equality of tints has been re-established, the angle through which the prism has revolved, read off on a graduated circle, gives the inclination of the required plane to the known plane. This mode of determining the zero, a process which for perfect accuracy ought to be repeated with each new set of observations, possesses the advantage of eliminating the personal equation of the observer. In examining a beam of any considerable magnitude, there will be found in different persons a tendency to think one part of the image darker than another, even when there is no real difference. With different observers, and even in the same person at different times, the part of the image thus preferred may be different, and if the zero were determined once for all this might occasion sensible error. But as in the method here given such a preference will equally affect the position of the zero, it can have no influence on the final result.

In the first prism which Jellett caused to be constructed the angle between the planes $C P$, $C P'$ was about 7° . With this prism the range of error in the determination of a plane of polarisation was $7'$, the light employed being the diffused light of the

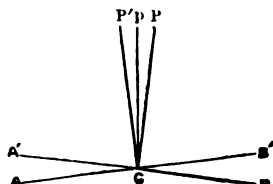
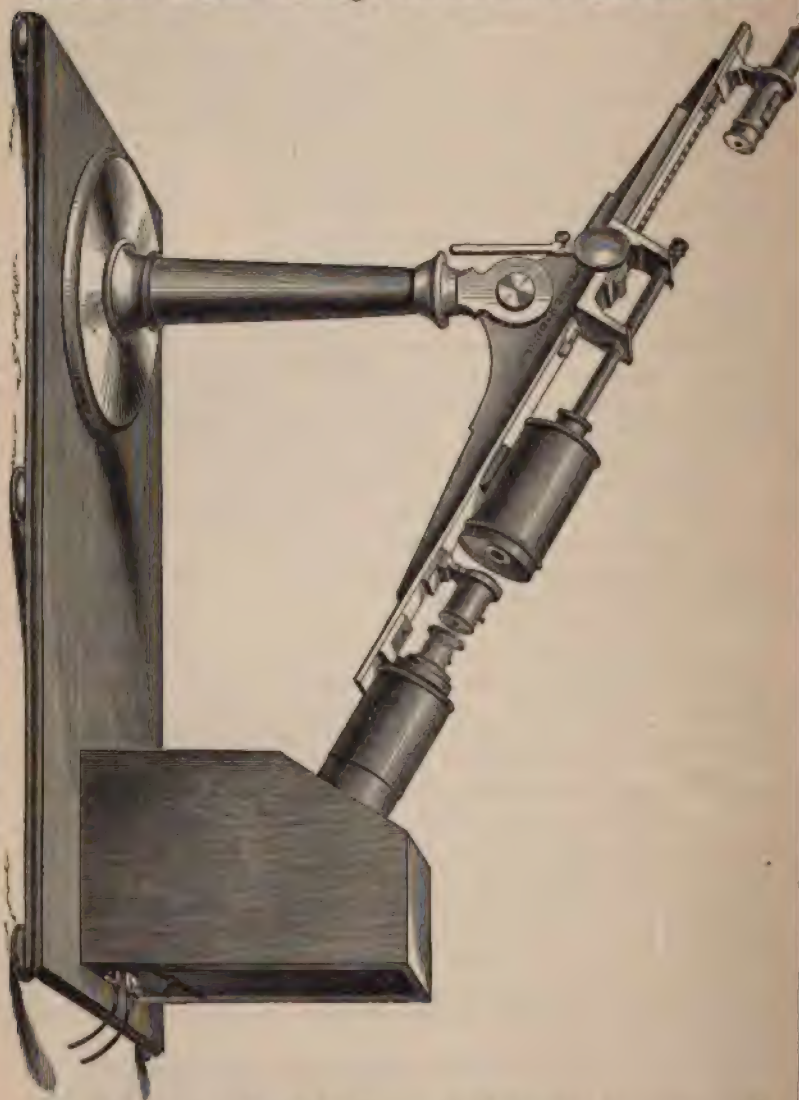


FIG. 4.—Diagram of angles of planes of polarisation in Jellett's Polariscopes.

sky. Although this was a very much smaller range than he had ever been able to obtain with a Nicol's prism, it seemed that a greater amount of accuracy might be obtained, and as the brightness of the image appeared to be too great, a prism was constructed in which this angle was but half of its former value.

FIG. 5.—Jellet's Polariscopes, arranged for use with oxyhydrogen light in box.



With this prism and with the same kind of light the position of a plane of polarisation could be determined to $1'$. With direct

solar light and a prism in which the planes are still closer, a greater degree of accuracy may certainly be obtained; in fact it can be shown that by diminishing this angle and increasing the brightness of the light, so as to preserve unchanged the intensity of the image, the sensibility of the prism will vary as $\cot. \frac{\theta}{2}$, θ being the angle in question.

The prism here described is fixed in the eyepiece or analyser of the apparatus, the general aspect of which is given in the accompanying fig. 5. But while the rotation of the prism necessary for determining the zero point is effected by little screws fixed to the tube a little below the ring by which the eyepiece is fixed to the beam on which the axis of the instrument is carried, the mechanical rotation of the analyser for the finding of any particular plane is altogether dispensed with, and this function is transferred to a fluid which has the power of turning the plane of polarisation in a direction opposite to that which it is intended to determine in the casual observation. This fluid may be any

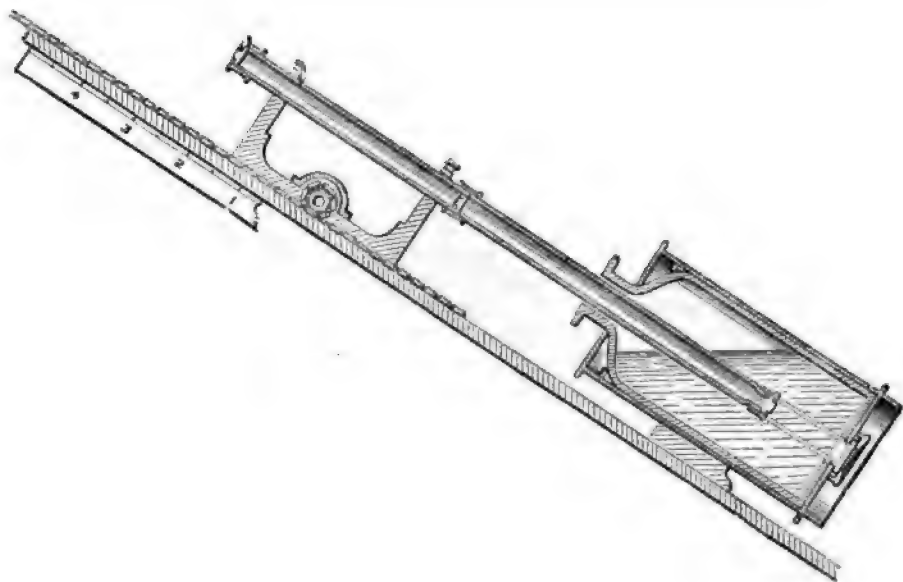


FIG. 6.—Jellett's Polariscope—Section.

polarising solution of stationary power. In the present instrument, however, right or left turning spirit of turpentine is used. Of this polarising turpentine the rotating index per inch, tenths, or hundredths of an inch is ascertained as expressed in per cents. of sugar contained in solution in the analysing tube. The analysing tube dips into and moves up and down in the turpen-

tine itself. This arrangement will be more intelligible by the aid of fig. 6.

The order of events in an actual analysis now is as follows:—

(1.) *Finding of the zero point.* A beam of parallel light produced in the closed box at the end of the apparatus, by means of the oxyhydrogen-calcium light and a compound condenser, is thrown in the direction of the optical axis of the apparatus. It passes first through the polarising prism. The polarised beam then enters the bottom of the turpentine bottle. The long tube containing water is pushed down to the bottom of the turpentine bottle, until its glass plate rests upon the plain surface of the inside of the turpentine bottle. The arrow of the indicator is placed upon the zero point of the scale attached to the side (of which a portion is represented in fig. 6), and the analysing eyepiece is now turned until the tints of the half-circles of its picture are equal. (2.) *Finding of the index of the turpentine as expressed in per cents. of sugar.* The tube containing water, and intended to contain the fluid to be analysed, is now filled with a solution of dextrose sugar containing 10 per cent. of sugar, which turns the plane of polarisation to the right. If the tube be replaced as before, the tints of the picture in the analyser will now be unequal. The tube carrying the sugar solution is now raised upwards by means of the milled-headed wheel, until the tints of the two halves of the picture in the analyser are again equal. By that means a column of oil of turpentine (turning to the left) will have been interposed between the sugar solution and the polariser (as shown in fig. 6), which turns the plane of polarisation as much to the left, as the tube full of ten percentic sugar solution turns the plane of polarisation to the right. Both polarisations will have completely neutralised each other. Supposing the arrow stand upon 1 of the scale, then a column of one inch of left-turning turpentine has been required to neutralise the polarisation of a solution of 10 per cent. of sugar in the tube. If now a solution containing either more or less sugar be placed into the tube, a longer or shorter column of turpentine will be required to neutralise its effects. And as the effect of a column of one inch (in the above example) is known to indicate 10 per cent., the effect of any length, or its sugar indication, can be found by the equation $1 : 10 = t : x$, in which t is the length of the turpentine column measured on the scale, and x the percentage of sugar contained in the problematical fluid in the tube. I have not entered into minor details of the construction of this apparatus, such as the chain in connection with the milled wheel by which the closed tube is moved up and down in the turpentine bottle, or the long lever attached to the milled wheel for delicate adjustment. These must be studied upon the apparatus itself, and like the entire apparatus itself will be found

to leave nothing to be desired in respect of mechanism. No other polarimeter approaches this instrument in accuracy for saccharometrical purposes, as with care it indicates 0.01 per cent. of sugar. But its disadvantages are that it requires powerful artificial light, that it is cumbrous and complicated and must be skilfully managed, and that it cannot yet be made to indicate the polarisation of any particular ray of light, say the yellow or the green, and it will probably be better not to attempt to complicate it with any arrangement for that purpose.

Wild's Polarimeter.—This instrument, represented in fig. 7, is very handy for general purposes in which only approximative results are required. It is held by the hand at K, and A is



FIG. 7.—Wild's Polarimeter.

directed towards the diffuse light of the sky, or a white cloud, a candle, lamp, or gaslight, while the eye is applied at F. At A the tube contains a Nicol's prism. At B a Savart's polariscope is fixed consisting of thick pieces of quartz with intermediate lenses and a wire cross of the shape represented in fig. 8. The eyepiece F carries a second Nicol's prism, which turns with the disk E, carrying the division of the circle on its circumference. For the greater convenience of manipulation a lever G is fixed in the disk. The zero point and nonius are immovable at D, and B C is the arrangement by which the handle is fixed to the instrument. I is a black disk, intended to further screen the eye from the direct light, and H is the tube in which the fluid to be

examined is placed. When the eye receives the transmitted light of the apparatus, while the divided circle is in any position

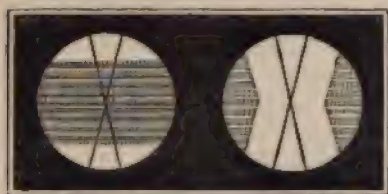


FIG. 8.—Wires and Field of Wild's Polarimeter.

except those where 0° , 90° , 180° , 270° are exactly incident with the zero mark of D, then a picture sketched in the left-hand circle of fig. 8 is seen, consisting of striæ of interference running horizontally through the entire field of vision. But when 0° , 90° , 180° , or 270° are placed exactly upon the zero point at

D, the transverse striæ are not visible in the middle of the field, where now the wire-cross alone is visible, as represented in the right-hand circle of fig. 8. If now the tube X is filled with any fluid possessing the property of circular polarisation, and is placed into the position indicated in the engraving, and if at the same time the zero point at D is made coincident with 0° of the rotating disk, the striæ of interference will be visible, and will only disappear after the disk E has been turned a little to the right or to the left. In case the fluid contained in the tube H causes a rotation above 5° , the striæ of interference only become weaker, but do not disappear entirely from the middle of the field of vision in any position. If the rotation was less than 5° , and the point has been attained at which, as in fig. 8, II., the interference striæ in the middle of the field of vision have disappeared, the observer may read the amount of rotation towards the left or right side which the fluid has effected by reference to the scale.

In case the rotation of the fluid amounts to more than 5° , it is advantageous to employ monochromatic light for determining the amount of polarisation. This may be done simply by fixing a plate of red glass before the aperture A, or using as the source of light a spirit flame the wick of which has been drenched with common salt. With such light the striæ by interference disappear at a certain position of the analyser, may the rotation be ever so great.

On the Alleged Occurrence of Sugar in Normal Urine.

It was originally stated by Brücke that all normal urine contained grape sugar. This view was supported by Bence Jones ("Journ. Chem. Soc." 1862), notwithstanding that he had been obliged to denounce one of the analytical methods adopted by Brücke as useless. Kühne ("Physiol. Chem." p. 516) accepted the statement as proved, and fortified it by a variety of additions. In consequence the proposition was accepted by many, notwith-

standing the opposition of Friedländer, Wiederhold, Meissner, and Babo (*"Zeitschr. ration. Med."* (3) vol 2), who showed by further experiments the invalidity of the alleged proofs of Brücke.

A similar state of things ensued with regard to the statement by Brücke, that under certain physiological conditions, such as the process of lactation in women, or under the influence of drugs, even more sugar was excreted in the urine than in health; this allegation was controverted by Leconte.

The entire question was in the year 1871 subjected to a thorough examination by Seegen (*"Sitzb. d. k. Akad. d. Wissensch."* Vienna, June 1871). He tested the value and delicacy of each of the commonly employed methods for showing the presence, or isolating, or estimating the quantity of sugar in urine, and came to the conclusion that the statements of Brücke, Bence Jones, and Kühne were a series of fallacies, and that normal human urine contained no sugar.

Seegen first discusses the value of Fehling's proceeding, and gives it, in general, preference to all others. When a notable quantity of sugar is present in the urine to be tested he admits the reaction to be immediate and final. But when sugar is present only in small quantity, the test becomes less striking, in this, that although a reduction of the copper evidently takes place, no cuprous oxide is precipitated. The particular features of the partial failure of the test Seegen describes as follows:—*(a)* The fluid becomes turbid on boiling, and changes colour to dirty green or dirty yellow; *(b)* the blue fluid becomes yellow or brown, and only after some standing a slight turbidity ensues—it becomes dichroic, being dirty yellowish-green in reflected, and brown in transmitted, light; *(c)* the blue fluid becomes wine-yellow, but remains clear and transparent—on standing it deposits flaky phosphates coloured slightly yellow or reddish-brown by cuprous oxide.

Seegen further says that when urine contains less than half a per cent. of sugar it cannot any longer be determined quantitatively with accuracy by Fehling's fluid; in some cases even urine containing one per cent. cannot be quantitatively examined. For the cupric solution on addition of urine becomes first of a dirty green colour, then a yellow or a brown precipitate forms which remains suspended in the fluid; the fluid does not become clear even after several hours of standing; the limit of the reaction, namely, the disappearance of the blue colour, cannot be ascertained.

This peculiarity had been observed by Seegen in the urine of diabetic patients whose condition had been improved by appropriate diet. As long as the patients excreted urine with from 3 to 5 per cent. of sugar the urine could be diluted tenfold with

water, and thus containing only 0.3 to 0.5 per cent. of sugar gave very exact results with Fehling's liquid. But when the urine originally only contained from 0.3 to 0.5 per cent. sugar, then this undiluted urine gave the turbid reaction which made quantitative analysis impossible. Further, urine from diabetics who excreted large quantities of fluid gave the most precise reaction, while urine from patients who excreted a small amount gave the turbid fluid. Seegen attributes this effect to the normal constituents of urine in concentrated solution: it is diminished or annihilated by dilution with water. Based upon a series of experiments, he denies the correctness of the surmises of Winogradoff (Virchow's "Archiv." 27) and of Kühne, that the complete deposition and even formation of cuprous oxyde in some forms of diabetic urine was prevented by a particular pathological ingredient, which neither could define. The body or bodies which cause this disturbance it is at present impossible to define; suspicion is directed towards the extractive matters; kreatinine in concentrated solution keeps red oxyde of copper in solution; ammonia, however, has no share in the effect.

With proper dilution 0.0017 grm. sugar dissolved in 5. c.c. of liquid could yet be shown to form suboxyde, and to make the urine turbid. Normal urine, to which 0.03 per cent. sugar had been added did not give a distinct turbidity with Fehling's test. Normal urine by itself does not do this, and therefore Seegen rejects the statement of Kühne, that normal urine contained as much as 0.1 per cent. of sugar. If any at all be present, the sugar in normal urine must be less than 0.03 per cent. Seegen then confirms the reducing effect upon copper solution of uric acid, already studied accurately by Meissner and Babo (*loc. cit.*). 0.003 grm. uric acid, dissolved in 10 c.c. of water, produce a red deposit in Fehling's liquid. Uric acid crystals and urates direct from urine do the same. Urine which is rich in uric acid undergoes the change described above under (b). The extractives prevent the deposition of the cuprous oxyde formed by uric acid in the same manner as they prevent the completion of the reaction from sugar in the forms of diabetes with small excretion of water.

The trisnitrate of bismuth and soda test is not a delicate test for small quantities, and cannot be applied for quantitative estimation at all. The caustic potash test, by formation of caramel, &c., the brown colour and characteristic odour, is also not applicable to quantitative determinations, and does not indicate with certainty small quantities.

Huizinga's (Pflüger's "Archiv." 1870, Heft. 10 and 11) modification of Hagar's mode of showing the presence of sugar in normal urine by treating it first with mercurous nitrate, then with sodic chloride, and lastly with hydrochloric and molybdic

acid, and relying upon the reduction of the latter to molybdate of molybdic oxide, which is blue, is shown by Seegen to be a mere fallacy. Many other organic matters contained in urine, *e.g.*, acetic acid, effect the same reduction.

In his discussion of the capabilities of the optical method of estimating sugar quantitatively, Seegen comes to the conclusion, that even in urine which has been decolorised by animal charcoal a quantity of sugar which is below 0.2 to 0.3 per cent. cannot be any longer estimated. This can, however, be admitted only for the more common and coarse sort of polarimeters, as it has been shown above that Jellett's polariscope will yet indicate rotations corresponding to 0.01 per cent. of sugar. He then passes over to the consideration of the fermentation test, and its various adaptations to quantitative estimations, notably the estimation of the carbonic acid evolved by weighing as well as by volume. Concentrated urine retarded or stopped the fermentation: in dilute urine it proceeded as in water; but sometimes more carbonic acid was obtained than corresponded to the sugar present in the fermenting liquid. The yeast alone was able to cause the evolution of some carbonic acid from urine. Consequently Seegen considers the fermentation test as not capable to show the presence of small quantities of sugar in urine. Bence Jones, Huizinga, and Lieben ("Ann. Chem." 1870) have relied upon showing the presence of alcohol in urine treated with yeast as a test for the previous presence of sugar. Bence Jones tested the distillate with chromic acid, Lieben with the iodoform test. These tests are void by two fallacies—first, yeast always yields a little alcohol on distillation by itself; secondly, urine always contains a matter which is not alcohol, and yet gives the chromic acid and the iodoform reaction.

In view of the impossibility of proving the presence of sugar in normal urine by reactions carried out in the presence of the ingredients of the urine, Brücke endeavoured to isolate the supposed sugar by two methods, one known as the sugar potash process ("Sitzb. d. k. Akad. d. Wissenschaft," vol. 29), and the other as the lead process (*ibid.* vol. 39, p. 10). He added four parts absolute alcohol to one part of urine, and then an alcoholic solution of caustic potash until the liquid was alkaline; the deposits which crystallised after twenty-four hours he assumed to be sugar potash. Seegen showed that to liquid thus prepared any quantity of sugar up to 1 per cent. may be added, and yet the deposit, if any ensues, will not contain sugar; the sugar remains in the alkaline alcohol; further, sugar potash is deposited only from alcohol not less than 90 per cent. strong, is not crystalline, not colourless, but appears as a yellow mass, which on exposure to air quickly becomes a brown varnish. The crystalline deposit obtained by Brücke may have been urate, as

it reduced copper solution. Seegen never obtained any crystalline, and never any deposit at all which reduced copper solution. Even after evaporation of saccharine urine, and extraction with absolute alcohol, this solution gave only a portion of the sugar contained as sugar potash. Even thus modified the process cannot be used for determining sugar quantitatively.

Brücke's lead process is the following:—The urine is precipitated with neutral plumbic acetate, the filtrate is precipitated with basic plumbic acetate, and to the filtrate ammonia is added. The third precipitate is said to contain the sugar in largest quantity, but the basic lead precipitate also is said to contain some. Now, as basic lead acetate produces no precipitate in sugar solution, Brücke assumes that the urine contains a substance which makes such a precipitation possible. In this manner the clear logic of facts is perverted by the most gratuitous assumptions.

However, Seegen shows that neither precipitate yields any sugar. Lehmann's proceeding of making sugar potash from alcohol extract, dissolving the sugar potash in water, neutralising with acetic acid, precipitating with plumbic acetate, decomposing with hydrothion, and proving presence of sugar in filtrate gave no better result. When Seegen dissolved 0.5 grm. of sugar in a litre of urine, he could recover two-thirds of it by means of ammoniacal lead precipitates; but 8 litres of urine gave a completely negative result, and therefore normal urine cannot contain as much as 0.006 per cent. of sugar.

In his paper on the glycosuria of suckling women ("Wiener Med. Wochenschr."), Brücke says, that although the urine in these cases gave reactions of sugar, he could sometimes not obtain sugar potash from it. This he explains by the hypothesis that the urine had contained a substance which prevented the precipitation of the sugar potash. The reader will remember that when the basic lead acetate precipitate contained a reducing body, this was caused by a hypothetical matter which propitiated an otherwise impossible precipitation. Seegen shows that neutral plumbic acetate precipitated no uric acid, basic acetate precipitated most uric acid, and ammonia added to the filtrate a little in combination with lead. Brücke's reducing substance, which he supposes to be sugar, is proved to be uric acid. Thus falls the objection which Brücke raised to the purification of the urine by neutral and basic lead acetate (not ammonia) previously to applying any optical or chemical test for sugar.

Seegen then shows the fallacy of Bence Jones' proceeding, which relied upon a reduction in the precipitate by ammonia in urine already treated by neutral and basic lead acetate. If his quantities had been true he would have proved the presence of only 0.0002 per cent. of sugar in normal urine.

Seegen thus arrives at the following conclusions :—

1. There is no reliable reagent for proving the presence in urine of very small quantities of sugar ; substances acting analogously to sugar cannot yet all be excluded.

2. Therefore all assumptions concerning the occurrence in urine, during physiological and pathological conditions, of small quantities of sugar cannot be considered as proved beyond doubt.

3. Normal human urine does not contain sugar in quantity sufficient for indubitable proof of its presence.

4. Normal urine contains small quantities of reducing substances. Whether or not a part of them is sugar cannot be determined by our present analytical means.

We may add that uric acid and pyrocatechin are fully sufficient to explain all the phenomena obtained by the lead precipitates.

Seegen then gives a means to remove the uric acid from urine, and obtain any small quantities of sugar which it may contain. The urine is filtered through animal charcoal as many times as may be necessary to decolorise it. The filtrate may be tested by Fehling's solution ; it is free from uric acid. The charcoal retains the uric acid and some sugar, but yields the greater part of the latter only to the first portion of water brought in contact with it. In this Fehling's solution gives the reaction. The charcoal retains some sugar, and the treatment by it must not precede quantitative determinations.

Note on Artificial Mellituria produced on Living Animals.—Since the discovery by Bernard of diabetes by brain lesion, medical literature teems with relations of fanciful experiments on animals, in the course of which "sugar" is said to have been excreted in the urine as a consequence of the experimental proceeding. It would be impossible to enumerate them, and a waste of time to refute any of these crudities. But it seems necessary to quote a few examples of the manner in which physiological periodicals are stocked. Bock and Hoffmann ("Archiv. Anat. und Physiol." Von Reichert and Du Bois-Reymond, 1871, 550) injected salt water into the blood of rabbits, and found "sugar" in the urine. Albumen also appeared, and later dropsy. Kuntzel ("Inaugur. Diss." Berlin, 1872) then produced the same effects by a number of other salt solutions. Külz (Eckhard's "Beiträge zur Anat. und Physiol." Giessen, vol. 6 (1872), Heft. 3) could not confirm the Bock-Hoffmann and Kuntzel experiments, when he tested the results, probably by the light of the criticisms furnished by Seegen. In particular he never obtained any rotation in the polarimeter. But he obtained reduction of copper, and therefore assumed the existence of an "optically inactive sugar." The salts which produced mellituria

in any number of rabbits failed to produce it in twenty dogs. Sodium acetate alone produced "sugar" in the urine of dogs; the others proved to be "glycogenetically inactive." The effect of these salts is said to be mediated by "nerve action." But Cyon and Aladoff (*Bullet. de l'Acad. Imper. des Sciences de St. Petersbourg*, 1871, Août 16, Nr. 4, 305) state that the urine of dogs contains sugar regularly as a normal ingredient. Division, or extirpation of the ganglion stellatum increases this natural glycosuria. Against these authors others again appear, such as the producers of the amyl-nitrite diabetes. And in all these laborious researches, voluminous statements, and lively controversies, the pivot of the levers is a paltry reaction, an abstraction of a little oxygen from a copper solution, never in a single instance even accumulated proof by divers reactions, never the isolation of the matter itself, the very existence of which is at issue.

The Urine in Diabetes Mellitus.

The following account of the general features of the urine in diabetes is collected from the experience of specialists, more particularly from the essay of Seegen ("Der Diabetes Mellitus," Leipzig, 1870).

When the urine contains appreciable quantities of sugar for a length of time, the occurrence is diagnostic of the disease known as diabetes mellitus. Of this disease the excretion of sugar is the most essential and patent result, though the cause of the presence of sugar in the blood and organs is more remote, and at present not explained. The excretion of sugar is thus also the most important symptom, and some pathologists are of opinion that all other symptoms of diabetes are only consequences of it. The quantities of sugar excreted in such cases vary from the smallest just appreciable amounts to 600 grm. in twenty-four hours. In general they stand in direct relation to meals, so that the urine containing the most sugar is found to be excreted in from three to four hours after a meal. In consequence of this relation more sugar is commonly excreted during the day than during the night. The quantity of sugar excreted stands in a direct proportion to the nature and quantity of the food taken. Pure animal food will cause the sugar in the urine to fall to less than 1 per cent., while starchy and saccharine food will cause it to rise to from 5 to 6 per cent., in extreme cases to 10 per cent. When little or no food is taken, *e.g.*, during febrile diseases, the urine of otherwise diabetic patients may contain no sugar, or give only doubtful indications of its presence. This may also happen with persons who present only a mild form of diabetes, and whose urine then contains no sugar in the morning. The urine of such patients should be examined from three to four

hours after a meal at which they have taken saccharine and amylaceous food.

With regard to diabetes it is particularly necessary to observe the rules laid down in the first chapter of this treatise concerning the collection of the total of the urine passed in twenty-four hours and analysis of an average specimen. The mere percentage of sugar in a chance specimen of urine may lead to erroneous views regarding the prognosis of the disease. But even the observation of the average quantity of urine and sugar contained in it during twenty-four hours is not by itself sufficient to guide to a correct appreciation of the prospects and present state of the patients; to obtain this it is necessary to know quantity and nature of the food consumed by the patient. Thus when a man excretes daily 50 grm. sugar, while he is strictly on a meat diet, his condition is much more serious than that of a man who excretes 400 grm. of sugar daily while taking amylaceous and saccharine food.

The quantity of the urine secreted is almost always greatly increased, and this symptom causes the patient to relieve himself more frequently, and the trouble connected with this necessity generally first directs his attention to his complaint. The quantity of urine excreted in twenty-four hours may amount to 7 or 8 litres; most diabetic patients discharge from 3 to 4 litres, but an almost equal number excrete not much more than healthy persons, namely, from $1\frac{1}{2}$ to 2 litres. Generally speaking, the quantity of urine stands in a certain ratio to the amount of sugar excreted. But sometimes the quantity of urine falls while the percentage of sugar rises.

There are cases in which an unusually large amount of urine is excreted, which contains only very little sugar. Thus a patient excreted 5600 c.c. with 0.8 per cent. sugar, at a later period the urine fell to 4300 c.c., and contained only traces of sugar. In a number of cases of diabetes with a minimum excretion of sugar no increase in the quantity of urine is observed, although the patients have a frequent desire to micturate. In these cases it is assumed that the sugar contained in the urine exerts an irritating action upon the bladder, and causes its frequent evacuation.

In many cases the polyuria seems to be the result of an irritation of the nerves and consequent congestion of the kidneys. It has been shown that a lesion of a certain part of the fourth ventricle of the brain, which is situated close to that part the lesion of which produces glycosuria, does produce polyuria. It is therefore probable that in most cases of diabetes exhibiting polyuria and glycosuria at the same time, both these localities of the fourth ventricle are irritated or injured at the same time, while in cases with prominent polyuria and little sugar, the one

region only is the principal seat of the irritation or injury. Excitement of the nervous system frequently produces polyuria, e.g. in hysterical spasmodic affection. The urine excreted under such circumstances has a low specific gravity, and contains but a small quantity of solids, thus showing that it is due to an independently increased secretion of water, in which excretory solid matters had little or no share. It is therefore possible that a continued state of irritation of the nerve centre in the medulla oblongata, which presides over the secretion of urine, may produce a continuously increased excretion of water. If, at the same time, there is going on in the body a considerable amount of desintegration by febrile or other diseased processes, then the bulky urine will also contain a large amount of solids. The symptoms of polyuria and glycosuria seem therefore co-ordinate to, and not interdependent upon, each other. But while they not rarely show this independence of each other, in most cases of diabetes the co-ordination is such that quantity of sugar and bulk of urine rise and fall together, particularly when the increase of the sugar is due to increased consumption of amylaceous and saccharine food.

The colour of the urine in diabetes of a high degree is very slight; it is pale yellow, or has a greenish tinge, and is all the more pale as it is perfectly clear. But there are a good many cases of diabetes in which the urine has an intensely dark colour, and these are mostly mild forms unaccompanied with polyuria. A dark amber or generally a deeper colour approaching the normal may be considered as a favourable sign with regard to prognosis.

The specific gravity of the urine is almost always very high, and sometimes rises even to 1060. On one occasion Seegen observed a urine with 10 per cent. of sugar which showed specific gravity 1065. However, ordinarily the average specific gravity of the diabetic urine of twenty-four hours fluctuates between 1030 and 1040. The specific gravity cannot be used as a means for determining the quantity of sugar. The urine of diabetic patients is always acid; and this reaction is not easily changed, even if the urine is allowed to stand for some days.

The quantity of uric acid seems to be small; rarely it exceeds 0.6 gm. per day, sometimes it is below 0.3 gm. Such quantities cannot be precipitated from large volumes of water. It is therefore necessary in such cases to condense the urine of twenty-four hours to a normal bulk in order to obtain data which can be compared with physiological conditions. When a diabetic urine is dark and deposits urates, it indicates a mild form of the disease.

Diabetic persons excrete as a rule more urea than healthy persons of equal weight. This is caused by their consuming

larger quantities of albuminous food to cover the deficiency arising from the excretion of sugar (Pettenkofer and Voit, "Zeitschr. f. Biologie," vol. 2, Heft. 4; vol. 3, Heft. 4). When a diabetic person eats flesh and fat in due proportion, he may, as in the case of the observers just quoted, even increase in weight by retaining some of the ingested albuminous matters in his body, and adding them to the constituents of his tissues. There is no proportion between the quantities of urea and sugar excreted. On the contrary, the highest amount of sugar may coincide with the lowest quantity of urea, and the reverse may happen. The quantity of urea is in direct proportion to the quantity of albuminous food eaten, and the quantity of sugar is in direct proportion to the quantity of amylon and sugar eaten with the food. To this rule only those cases of diabetes apparently form an exception in which, notwithstanding an exclusively albuminous diet, relatively large quantities of sugar are produced. Such a case Seegen terms a hyperproduction of amylon and respectively sugar at the expense of the albuminates.

The quantities of other ingredients of diabetic urine have been so little examined that no general statements can be made regarding them.

In some cases of chronic diabetes albumen appears in the urine; but casts of the tubules as in idiopathic kidney disease seem to be so rare in these cases, that the albumen of diabetes seems to require an explanation different from that of chronic nephritis. A case of diabetes accompanying paralysis is under my observation, in which the urine has been strongly albuminous for many years, without the disease having made any progress; there are no casts of the tubules, and no oedema ever shows itself. In few cases only is there a coincidence of Bright's disease with diabetes.

of turning the plane of polarisation to the right, like grape sugar.

Physiological and Pathological Significance of Dextrine.

The occurrence of dextrine in the urine of a previously diabetic patient would indicate an important change in the diseased function; the diseased process would appear to be arrested half way; starch would be only isomerised, but not hydrated. The disease would indeed have to be considered as one analogous to, but differing from saccharine diabetes, and have to be described as diabetes dextrinicus. It is not impossible that this modification of diabetes may occur more frequently, just as the modification does sometimes present itself in which the place of sugar is in part or entirely taken up by inosite. Dextrine has been found in the blood, in the juice of flesh (once in considerable quantity in horse-flesh), and in the lungs and spleen. Thus it is proved that there is no obstacle to its distribution in the body. We must, however, wait for further observations of its occurrence in urine, in support of those of Reichard, before we can assume its appearance to be other than a sporadic phenomenon.

CHAPTER LI.

INOSITE, $C_6H_{12}O_6$.

HISTORY, LITERATURE, AND OCCURRENCE.

THIS hydrocarbon was discovered by Scherer ("Ann. Chem." 73 (1850), 322) in the mother-liquor of kreatine, obtained from the juice of the muscle of ox heart. Cloetta ("Ann. Chem." 99, 289) found it in the parenchyma of most organs of the animal body, the lungs, spleen and kidneys, and sometimes, as he believes, in the urine of patients suffering from Bright's disease. Vohl ("Ann. Chem." 99, 125) discovered a new kind of sugar in green French beans, *Phaseolus vulgaris*, and termed it phaseomannite. But he afterwards recognised the identity of this body with inosite ("Ann. Chem." 101, 50). He also found it in the urine of persons who were reported to be convalescent from diabetes mellitus. It was found to be a normal ingredient of the brain in man and animals (Müller, "Ann. Chem." 103 (1857), 131), and of many plants, such as the common cabbage, and the juice of grapes (Hilger, "Ann. Chem." 160, 333).

Mode of Obtaining.

The inspissated extract of flesh, or of any of the organs mentioned, from which kreatine has been obtained, is mixed with dilute sulphuric acid until all baryum is precipitated; it is then shaken several times with ether to remove volatile acids and lactic acid, and thereupon mixed with strong spirit until it becomes turbid. At first potash salts begin to crystallise, which may be removed, but on further addition of spirit inosite crystallises; the mother-liquor is now poured off, the crystals are separated first by picking them out, next by dissolving them in a little warm water, which dissolves the inosite quicker than the alkaline salts, and deposits it on cooling in crystals.

From the brain inosite is best obtained by extracting the hardened and comminuted brain with hot alcohol, concentrating the alcoholic extracts gradually until all phosphorised and nitro-dised matters (kaphaline, myeline, lecithine, cerebrine, phren-
a, kerasine, and cholesterine) are deposited, and the extract all alcohol. This now watery extract is treated with

sulphuric acid and ether to remove lactic and other acids. From the exhausted liquid the sulphuric acid is removed by caustic baryta. To the alkaline filtrate basic lead acetate is now added as long as a precipitate is produced. This is washed with water, decomposed with hydrothion, and evaporated at a gentle heat; when it is sufficiently concentrated, absolute alcohol is added until the mixture is turbid, and it is then allowed to stand. Inosite crystallises, which is isolated from the mostly acid mother-liquor, pressed between folds of bibulous paper, redissolved in water, boiled with a little animal charcoal, and again allowed to crystallise with the aid of alcohol. White shining crystals in the shape of needles are thus obtained, consisting of pure inosite. Another mode of isolating inosite has been described by Cooper Lane (*"Ann. Chem."* 117, 118), which is, however, much less convenient and certain than the lead process just described.

Physical and Chemical Properties.

Crystallised inosite is a dihydrate, $C_6H_{12}O_6 + 2H_2O$, its forms belong to the klinorhombic system, the typical crystals being probably klinorectangular prisms. The crystals mostly group themselves together; more rarely they are single, and then become sometimes from a quarter to three-eighths of an inch long. When exposed to the air they decay by losing water of crystallisation, and in vacuo over sulphuric acid, or at 100° become anhydrous. They taste purely sweet, are easily soluble in 6 parts of water of 19° , little soluble in strong spirit, insoluble in alcohol or ether. From the solution in boiling spirit, almost the whole of the inosite crystallises on cooling in small glistening particles, which are very much like cholesterine. It has no effect upon a polarised beam of light.

Inosite is not changed by boiling with dilute sulphuric or hydrochloric acid, or with caustic alkali. But when it is heated with hydrochloric acid it is easily transformed into an uncrystallisable matter. Treated with highly-concentrated nitric and sulphuric acid it yields hexanitrited inosite, $C_6H_9(NO_2)_3O_6$, a colourless substance, insoluble in water, soluble in alcohol. The mother-liquor of this body contains a second product, trinitrited inosite, $C_6H_9(NO_2)_3O_6$. When heated above 210° it fuses to a clear fluid, which, when cooled down rapidly, crystallises in needles, but when allowed to cool slowly, sets into a horn-like amorphous mass. When exposed to a stronger heat, inosite burns with a lighting flame, without leaving any residue.

A concentrated solution of caustic potash produces no change of colour on boiling with a solution of inosite; no change takes place when it is boiled with Fehling's solution; with bile and sulphuric acid inosite does not yield the reaction for sugar. It is not capable of undergoing vinous fermentation. But a solution

of it treated with rotten cheese and chalk at a temperature of about 25° to 40° for some length of time is transformed into lactic acid, which expels the carbonic acid of the chalk, and as hydrated lactate of calcium, causes the mixture to become a stiff paste. If the fermentation is allowed to continue beyond this point, the lactate is, by a new process, transformed partially or entirely into butyrate.

If a solution of inosite, or a mixture containing inosite, is evaporated in a platinum spoon to near dryness, and the residue moistened with ammonia and some calcic chloride, and then again cautiously evaporated to dryness, a vivid rosy colour is produced; this reaction admits of the diagnosis of one-fiftieth of a grain of inosite.

A solution of inosite, when mixed with a solution of basic lead acetate, forms, immediately on warming, slowly at the ordinary temperature, a clear transparent gelatinous mass, which undergoes no change when kept secluded from the air. It is this compound by the formation of which inosite can be most conveniently removed from complicated animal liquids, such as the extracts of organs or urine.

The lactic acid from inosite by fermentation is mostly the ordinary lactic acid, the lime salt of which contains 29.2207 per cent. of water of crystallisation, while its zinc salt contains 18.1781 per cent., as was specially proved by Vohl ("Ber. Deutsch. Chem." G. 9 (1876), 984), but is perhaps sometimes, as has been stated by Hilger ("Ann. Chem." 160, 383), sarcolactic or flesh lactic acid, whose calcium salt contains 27.09 per cent., and whose zinc salt contains 12.9011 per cent. of water of crystallisation. A watery solution of the calcium lactate from inosite, when treated with an excess of neutral zinc chloride, gives immediately a heavy crystalline precipitate of zinc lactate, which can be purified by repeated recrystallisation from hot water. On the other hand, a cold saturated solution of sarcolactate of calcium when treated with a 10 per cent. solution of neutral zinc chloride never gives a precipitate of zinc lactate. By this reaction the two forms of lactic acid can be distinguished and separated from each other.

The lactic acid from inosite, when distilled with a mixture of potassic dichromate and sulphuric acid, yields a distillate containing acetic and formic acid. The residue in the retort contains no malonic acid. This reaction also is characteristic of ordinary lactic acid by fermentation (*see* Notes on Sarcolactic Acid by Erlenmeyer, "Ann. Chem." 158, 262).

Inosite in the Urine of Diabetic Persons.

Claëtta had found inosite in the urine of a patient with, Bright's and Vohl then found inosite in the urine of persons who used to have recovered from grape sugar diabetes.

Külz examined the urine from eight diabetic persons, but could find inosite in small quantity only in one. He then caused five diabetic patients to eat large quantities of green beans, to see whether any inosite appeared in the urine after this diet. But none appeared, and even the urine of the patient, who had before taking to bean diet excreted a little inosite, during and after the diet was found free from it.

The same author ("Centralbl. Med. Wissensch." 1875. Nr. 54) produced so-called diabetes in a rabbit by injecting into its jugular vein 25 to 30 c.c. of a solution of common salt in water every five minutes during 5½ hours, so that the rabbit must have received into its circulation 1575 c.c. of fluid. There were obtained 1079 c.c. of urine, from which 32 milligram. of inosite were isolated.

Gallois reports to have examined the urine of 102 patients, and to have found inosite in 7 of them. Out of these 102 there were 30 diabetes, and of these 5 showed varying quantities of sugar besides some inosite, out of 25 cases of albuminuria 2 excreted some inosite. Gallois relies upon the following test for the identification of inosite:—He evaporates the liquid to be tested for inosite in a porcelain dish to the bulk of a few drops, and then adds a small drop of a solution of mercuric nitrate. This produces a yellowish precipitate. When this is spread as far as possible over the surface of the porcelain, and the dish is further heated with great caution, there remains as soon as all fluid is evaporated, and provided that no excess of reagent has been added, a residue, which is whitish-yellow at first, but soon becomes more or less dark red, according to the quantity of inosite present. The colour disappears when the dish gets cold, but reappears on reheating it gently. The reaction is not produced by uric acid, urea, amylum, milk sugar, mannite, glykokoll, taurine, cystine, and glykogen. Albumen assumes a rose colour, sugar becomes black under the reaction (Gallois, "De l'Inosurie," Paris, 1864; Schultzen, "Arch. f. Anat." 1863, 1, 23). When this reaction is instituted with pure crystallised inosite from brain, no precipitate is produced, but the pink reaction is obtained as stated. A minimum of mercuric nitrate is required, and evaporation on the water-bath makes the appearance of the red colour more secure. If when the colour has appeared the dish is overheated to the slightest degree, the mixture undergoes a kind of sudden decomposition, though without the appearance of flame, or incandescence, and becomes black.

CHAPTER LII.

LACTIC ACID, $C_3H_5O_2$.

OCCURRENCE, HISTORY, AND LITERATURE.

LACTIC acid was discovered by Scheele in sour milk. It is found in the brain and the muscles of man and animals. It has been found in the urine under various circumstances by Lehmann; other chemists, however, *e.g.*, Liebig, Pelouze, and Gregory, have never been able to find it in urine. Under certain conditions it is formed during the fermentation of sugar, and consequently is found in many fermented acid liquids, particularly the juice of fermented cabbage. It has been discovered under pathological conditions in the urine, thus after poisoning by phosphorus, in acute malignant jaundice (Schultzen and Riess, on acute phosphorus poisoning); in trichiniasis (Simon and Wibel, "Ber. Deutsch. Chem." 6, 1871, 139); and in osteomalacia by Lehmann, Scherer, and Marchand, and lately by Moers and Muck ("Deutsch. Archiv. f. Klin. Med." 5, 485).

Mode of Obtaining.

The acid is most conveniently obtained by the so-called lactic acid fermentation of glucose, cane sugar, milk sugar, dextrine or inosite, under the influence of putrid caseine in the presence of calcic carbonate at a higher temperature. The following prescription by Bensch ("Ann. Chem." 61, 174) may be followed with advantage:—6 parts of cane sugar, $\frac{1}{8}$ th part of tartaric acid, 8 parts of sour milk, $\frac{1}{2}$ part of old cheese, and 3 parts of levigated chalk, are mixed with 26 parts of water and exposed to a temperature of 32°. In the course of ten or twelve days the mixture is transformed into a semi-solid mass of lactate of lime. This is boiled with 20 parts of water and $\frac{1}{8}$ th part of caustic lime; the mixture is filtered while boiling hot, and then gently evaporated. From the concentrated solution lactate of lime in granules is obtained after some days' standing. The salt is collected in a bag, and pressed in several folds of linen, to free it from liquor. It is then again dissolved in twice its weight of water, and decomposed with $\frac{1}{8}$ th parts of sulphuric acid. The gypsum is removed by filtration, and the acid fluid

saturated with $\frac{1}{10}$ ths of carbonate of zinc. The crystallised zinc salt is then decomposed by sulphuretted hydrogen, and the filtrate is evaporated by heat, lastly in vacuo. The lactic acid thus obtained may be further purified by solution in ether.

Lactic acid is also formed by digesting a 2 per cent. grape sugar solution with a piece of the mucous membrane of a pig's stomach at 30° to 40°. But whereas in the former process the lactic acid obtained is always the optically inactive zymolactic acid, the acid prepared by the present process is sometimes entirely, and in about half the preparation contains considerable quantities of the optically active sarcolactic acid. They may be separated by fractional crystallisation of their zinc salts from water in which sarcolactate is more soluble than zymolactate. (Maly, "Ber. Deutsch. Chem." G. 7 (1874), 1567).

Liebig's Method of Obtaining Lactic Acid from the Juice of Flesh.—The mother-liquor from which kreatine has crystallised is evaporated a little more, and then gradually mixed with small portions of alcohol, until it assumes a milky turbidity. After a few days' standing the inosinates have crystallised. The mother-liquor from this crystallisation is again evaporated in the water-bath, and the residue treated with alcohol, which dissolves all the lactates. The solution is separated from the insoluble syrup, and the alcohol is evaporated to a syrupy consistence. This syrup is now mixed with an equal volume of dilute sulphuric acid (composed of one volume of concentrated acid and two volumes of water), or with a solution of oxalic acid of equal strength; of the latter so much must be added that a crystalline precipitate ensues. The mixture is immediately treated with three or four times its volume of alcohol. The sulphates and oxalates are thereby precipitated, lactic acid remaining in solution. To this solution ether is added, until the addition of a new portion does not produce a fresh turbidity. The precipitate is separated from the fluid by filtration, the filtrate freed from alcohol and ether by distillation and evaporated on the water-bath to a syrupy consistence. This syrup is mixed with half its volume of alcohol, and then five times its volume of ether is added, whereby an almost pure solution of lactic acid in ether is obtained. The ether is evaporated, the residue is treated with milk of lime; the lactate of lime obtained after filtration and evaporation is washed with alcohol, and by recrystallisation, and, if necessary, treatment with animal charcoal, is obtained perfectly pure. From it lactic acid may be obtained as above.

Wislicenus ("Ann. Chem." 167 (1873), 304) obtains the lactic acid from extract of flesh as follows:—One part of extract is dissolved in 4 parts of warm water, and to the solution 8 parts of alcohol of 90 per cent. strength are gradually added. The alcoholic liquid is decanted from the brown precipitate. The latter is

dissolved once more in 2 parts of warm water, and again precipitated by from 4 to 5 parts of alcohol. The united alcoholic extracts are distilled and evaporated to a thin syrup. Gradual addition of 3 to 4 volumes of alcohol now produces another precipitate, which is removed. The solution, again freed from alcohol by distillation, is strongly acidified with dilute sulphuric acid, and extracted 6 times with an equal volume of ether. The ethereal extracts leave on distillation the lactic acid, mixed with some sulphuric acid and impurities. They are dissolved in a little water, and boiled with some lead carbonate; the filtrate is treated with hydrothion; the filtrate from the lead sulphide is boiled in an open dish, and then boiling saturated with zinc carbonate. The clear solution of the zinc salt is concentrated until, on cooling, it begins to deposit crystals, and is then quickly mixed with from 4 to 5 times its volume of alcohol of 90 per cent. The mixture, clear at first, becomes soon turbid, and deposits a voluminous pulp of minute crystals, which on stirring collect to a denser deposit. This is collected on the filter, washed with alcohol and pressed. The alcoholic filtrate on evaporation leaves a yellow syrup, from which some crystalline salt is deposited, particularly if absolute alcohol is gradually added. In this latter solvent the zinc salt of the second lactic acid dissolves, which crystallises only with great difficulty, and has formed an impurity in all preparations of sarcolactic acid described and handled by previous observers. The quantities of this latter salt are always small in comparison to those of the crystallised salt if American extract is used. If beef which has been hung for some days is employed, more of this second lactic acid is obtained. The relatively largest quantities are obtained from pathic collections of liquid in the human and animal body. The crystallised zinc salt must be dissolved in water and precipitated by alcohol repeatedly to free it entirely from the second salt. By decomposition with hydrothion the free sarcolactic acid is obtained, and finally purified from traces of zinc salt by solution in ether. In this manner 100 parts of extract of flesh yield two parts of pure zinc salt.

From alanine, which is commonly considered as amido-propionic acid, $C_3H_7NO_2$, lactic acid is obtained by treatment with nitrous acid in watery solution. The latter yields the lactic acid to ether, and this on evaporation leaves the acid ready for transformation into zinc salt. This reaction exhibits lactic acid as oxypropionic acid, or propionic acid, $C_3H_6O_2$, in which an atom of hydrogen is substituted by hydroxyle, $C_3H_6O_2 - H + HO = C_3H_6O_3$, just as the reaction by which alanine is formed, exhibits this body as amido-propionic acid, $C_3H_6O_2 - H + NH_2 = C_3H_7NO_2$.

Lactic (sarcolactic) acid is also obtained by the same process from the dinitrogenised derivative described in another chapter,

which occurs in normal and abnormal urine of man and animals.

Mode of Ascertaining the Presence of Lactic Acid in Urine.—The urine is evaporated on the water-bath to a syrupy consistence, and the residue treated with an alcoholic solution of oxalic acid. Oxalate of lime, potash, soda and urea, are thereby precipitated; the solution contains hydrochloric, phosphoric, and oxalic acids, and, if any be present, lactic acid. This solution is now treated with an excess of hydrated oxyde of lead, and the precipitate of chloride, phosphate, oxalate, and the excess of the oxyde of lead is separated from the fluid by filtration. The fluid, containing lactate of lead, is treated with hydrothion, and the filtrate after boiling with oxyde of zinc and filtration, on evaporation and standing, yields crystals of lactate of zinc. From this different salts, or the acid itself, may be prepared.

In consequence of the extremely minute quantities of lactic acid to be obtained from the animal fluids, Lehmann adopts the following method, with a view of studying the forms of the different salts under the microscope. The impure lactic acid from the alcoholic extract of the matters treated with sulphuric or oxalic acid, is treated with baryta water, and the excess of the baryta removed by carbonic acid; the solution of lactate of baryta is evaporated to the consistence of a syrup, treated with alcohol, filtered, again evaporated, and then allowed to stand for some time, in order that any other baryta salts may crystallise. If butyric acid were present in the urine, it would at this stage be obtained from the solution. The filtrate, or, if there was no crystallisation, the fluid, is dissolved in water, and decomposed with a solution of gypsum; the fluid from which the sulphate of baryta has been removed by filtration is strongly concentrated, and, on examining it under the microscope, the double brushes of lactate of lime may be easily distinguished from the crystals of gypsum. On dissolving these crystals of lactate of lime in alcohol, and adding sulphate of copper to the alcoholic solution, the fluid, after standing for some time (in order that the excess of sulphate of copper and the gypsum that is formed may separate as completely as possible), is evaporated so as to crystallise, and the crystals of lactate of copper are then microscopically examined. If, by the above process, we do not obtain distinct and measurable crystals, we must dissolve the residue in a little water, and, after boiling it to remove any butyric acid that may yet remain behind, filter and concentrate it. Into this concentrated solution of lactate of copper a small bar of zinc is placed. The zinc soon becomes covered with crystals of lactate of zinc, which may be identified under the microscope. If an accurate crystallometric investigation cannot be instituted, we must precipitate the solution of the zinc salt with a boiling

solution of protochloride of tin, and allow it to stand for some time; on then making a microscopical examination, we shall find clusters of crystals, in groups of thick rhombic plates, lying close upon each other. The demonstration of the different salts may thus serve to show the presence of lactic acid. If there be sufficient material, the atomic weight should be determined by an elementary analysis.

Moers and Muck (l. c.) proceeded as follows:—The fresh urine was made feebly alkaline with milk of lime, boiled, filtered, and evaporated in the water-bath to a syrupy consistence. The residue was extracted with alcohol, and the filtrate mixed with dilute sulphuric acid. After removal of the gypsum, the filtrate was much concentrated, and then mixed with water and zinc oxyde. Filtered from the excess of the zinc oxyde the liquid was evaporated, and from the residue the zinc lactate was extracted by alcohol. On evaporation of the solution crystals were obtained which were fit for microscopic examination.

Schultzen and Riess extract the lactic acid in urine, which occurs after poisoning with phosphorus as follows:—The urine is concentrated on the water-bath, and while hot precipitated with alcohol of 95 per cent. The alcoholic solution after twenty-four hours is decanted from the deposit, evaporated to a syrup, acidified with dilute sulphuric acid, and fully extracted with ether. The residue from the ether is dissolved in water, filtered, precipitated with neutral lead acetate, filtered; the filtrate is treated with hydrothion, filtered, and evaporated repeatedly to expel acetic acid. The colourless liquid so obtained is saturated with baryum carbonate, filtered, evaporated to a syrup and precipitated by alcohol. The pasty mass gradually becomes granular; its watery solution with zinc sulphate gives zinc sarcocollate in crystals, with 12.9 per cent. of water of crystallisation and 26.74 per cent. Zn.

Physical and Chemical Properties.

Lactic acid is a colourless, syrupy liquid, of a strongly acid taste. Its specific gravity is 1.215. It is soluble in any proportions in water, alcohol, and ether. When its solution in water is heated, a part is volatilised with the vapours of water; the greater part of the acid, however, at a temperature of 130° , loses half a molecule of water, and, doubling its molecular weight, is transformed into the anhydrous modification, which on cooling solidifies into a firm, yellowish mass of the formula $C_6H_{10}O_5$. This fuses already at a temperature below 100° ; when boiled with water it becomes again converted into the ordinary hydrated lactic acid. If the acid is heated to 260° , the loss of a molecule of water transforms it into *lactide*, $C_3H_4O_2$. This substance occurs as a *lactide*, and from its alcoholic solution crystallises in white,

glistening, rhombic plates. When kept in contact with water for some time it is also converted into lactic acid. On being heated rapidly, lactide is decomposed into aldehyde and carbonic oxide.

Wislicenus ("Ann. Chem." 164, 181) states that lactic acid of the formula $C_3H_6O_3$ does not exist as a pure preparation, and that already at the ordinary temperature it forms anhydride and lactide. As far as is described the lactic acid specimens obtained from the different sources quoted behave as if they were one and the same body. But on further inquiry, particularly by means of decomposition and the analysis of calcium and zinc salts in their hydrated state, it is found that the lactic acid obtained by the fermentation of different sugars differs from the lactic acid contained in the flesh; it is further maintained that the acid obtained from the flesh consists actually of at least two lactic acids; and that in addition there is a fourth lactic acid obtained by chemical synthesis. The lactic acid of fermentation can be produced from the lactic acid from flesh. We have therefore here to deal with an important case of isomerism, of which at least two terms were believed to be well understood. The fermentation lactic acid was said to contain the radical ethylene, and was therefore also termed ethylene lactic acid; whereas the flesh, or sarcolactic acid, was said to contain the radical ethylidene, and was termed ethylidene lactic acid. The acid, $C_3H_6O_3$, obtained from glycerin-iodopropionic acid, termed by Heintz ethylene lactic acid, although isomeric with lactic, had better be termed hydracrylic acid, because on thermolysis it decomposes yielding water and acrylic acid (Wislicenus, "Ann. Chem." 166 (1873), 3). By oxydation with silver oxide it yields carbonic acid, probably carbacetoxylic, glykolic, and oxalic acid, but not glyceric or acetic; by fusion with caustic alkali, formic and acetic acid. The synthetical ethylene lactic acid, produced from ethylene cyanhydrine, can be obtained pure with very great difficulty only, as its salts scarcely crystallise. According to Wislicenus this acid is identical with the second lactic acid, occurring in smaller quantity in the mixture of two lactic acids hitherto termed sarcolactic acid.

The lactic acid which occurs in flesh in the largest quantity, and yields a zinc salt with 2 molecules and a calcium salt with $4\frac{1}{2}$ molecules of water of crystallisation, is, according to Wislicenus, ethylidene lactic acid. Heintz agrees in this conception in so far that he admits a part of the sarcolactic acid to be ethylidene lactic acid; but another part he assumes to be (what he terms ethylene lactic acid, namely) the above-described hydracrylic acid ("Ann. Chem." 157 (1871), 314).

The four assumed isomers of the formula $C_3H_6O_3$ are therefore

(1) fermentation lactic acid, also termed ethylene lactic acid; (2) principal flesh lactic acid, also termed ethylidene lactic acid; (3) second flesh lactic acid, or synthetical ethylene lactic acid; (4) hydracrylic acid (termed by Heintz ethylene lactic acid).

Erlenmeyer ("Ann. Chem." 158, 262) could not confirm Wislicenus and Heintz as to the invariable existence of two lactic acids in the sarcolactic acid, and explained the results of these authors as possibly caused by an over-saturation of the solution of the zinc salt, to which he shows the compound to be prone. He never obtained malonic acid by oxydation of sarcolactic acid (which had been so obtained by Dossios), and therefore is inclined to admit that flesh may contain sometimes, but not always, two different isomers of lactic acid.

Wislicenus believes that the preparation of either the synthetical ethylene lactic acid or of the second sarcolactic acid (both of which he believes to be identical) in the pure state is so difficult a matter as to be almost impossible. He gives certain proofs for their identity, but they are mostly negative, such as the amorphous and syrupy conditions of salts, and the solubility in almost absolute alcohol, and leaves it to be surmised that the malonic acid, which was formed by his pupil Dossios under his eyes, from crude sarcolactic acid, was derived from this ethylene sarcolactic acid. But as the acid was only obtained in small quantity, and from a crude product, its use for structure formulæ is still less justified than it was for the purpose for which it has been used so many years.

Salts of Fermentation Lactic Acid (Zymolactates).

Zymolactate of calcium, $2(\text{C}_3\text{H}_5\text{O}_3)\text{Ca} + 5\text{H}_2\text{O}$, obtained by saturating the acid with carbonate, crystallises in granular masses, which under the microscope present a radiary arrangement of needles, or bundles of needles, which are united at their base like two camel hair pencils cut from the handle just above the tie of the hair. It is by these pencils that it is proposed to effect the microscopic diagnosis of this salt. It is little soluble in cold water and in alcohol, but soluble in all proportions in these liquids at the boiling heat. In the crystallised state it contains 29.22 per cent. of water of crystallisation, whereas sarcolactate of calcium contains 27.09, and not 24.83 per cent. as formerly maintained.

Zymolactate of zinc, $2(\text{C}_3\text{H}_5\text{O}_3)\text{Zn} + 3\text{H}_2\text{O}$, obtained by boiling dilute lactic acid with zinc oxide, is soluble in 6 parts of boiling, and 58 parts of cold, water. From its hot solution it crystallises easily on cooling in form of four-sided prisms, with oblique terminal planes. Small specimens assume a dumb-bell or oval shape of agglomeration of needles. It is nearly insoluble in alcohol, either hot or cold. The crystals contain 18.18 per cent.

of water of crystallisation, while sarcolactate contains 12.90 per cent.

Zymolactate of copper, $2(\text{C}_3\text{H}_5\text{O}_3)\text{Cu}$, crystallises in sky-blue little warts, and is soluble in 6 parts of cold water and in 115 parts of cold and 26 parts boiling alcohol.

Salts of Sarcolactic Acid (syn. Paralactic Acid, Heintz).

Sarcolactate of calcium, $4(\text{C}_3\text{H}_5\text{O}_3)2\text{Ca} + 9\text{H}_2\text{O}$, is very similar in its external appearance to the zymolactate, and is produced like it. It is, however, less soluble in water, and its crystals contain 27.09 per cent. (and not 24.83 per cent. as formerly supposed) water of crystallisation. This leads to 9 molecules of water in 2 molecules of salt.

Sarcolactate of zinc, $2(\text{C}_3\text{H}_5\text{O}_3)\text{Zn} + 2\text{H}_2\text{O}$, requires 17.5 parts of water for solution at 15° , and is therefore much more soluble in water than the zymolactate, which requires 58 to 63 parts; its crystals contain 12.90 per cent. water of crystallisation. The salt is deposited from a hot solution in a loose mass of separate crystals, which are short, hard, shining prisms; these crystals are the larger the slower the evaporation of the liquid has taken place. When finely powdered they give up their water of crystallisation at 100° to 105° in about an hour, and then remain unchanged at 170° to 180° . One part of crystallised salt requires about a thousand parts of boiling absolute alcohol for solution; cold alcohol dissolves even less. The statements in chemical works concerning a greater solubility in water and alcohol are due to observations on over-saturated solutions, which may be diagnosed by dropping a few small crystals into them, and observing how they immediately engender crystallisation.

Transformation of Sarcolactic into Zymolactic Acid.

Strecker ("Ann. Chem." 105 (1858), 313) showed that sarcolactic acid, when heated to 130° to 140° , is transformed into the anhydride of zymolactic acid, and by boiling with water the latter is then changed into the zymolactic acid itself. In the actual experiment the first watery distillate is unchanged sarcolactic acid; the remaining anhydride must be heated during several days to 130° in an oil-bath before it is entirely transformed into zymolactic anhydride. When the fusion is effected at 150° , in a current of dry air, lactide is sublimated, which after purification has the fusing point of 124.5 , the same as pure lactide from zymolactic acid. This lactide also, on being boiled a long time with water, yields pure zymolactic acid and its pure zinc salt.

Polarising Phenomena of the Anhydrides of Sarcolactic Acid.

The free sarcolactic acid when dried over sulphuric acid in vacuo during 21 months is transformed into a mixture of lactic

acid, $C_3H_6O_3$ (16.50 per cent.); anhydride, $C_6H_{10}O_5$ (84.19 per cent.); and lactide, $C_3H_4O_2$ (16.04 per cent.). The solution of this mixture turns the plane of polarised light to the left, $(\alpha) = -85.93^\circ$. It is probable that all three products on treatment with water are transformed back into sarcolactic acid. The transformation into zymolactic acid seems dependent upon heat.

Polarising Phenomena of Sarcolactic Acid.

The watery solution of sarcolactic acid shows a considerable polarisation to the left. This power is suddenly and greatly diminished after every addition of water, but on standing it rises again, without, however, reaching its former value. The diminution of specific rotatory power by dilution is the greater, the more concentrated was the solution used for dilution, that is to say, the greater was the dilution in proportion to the strength of the original solution. These changes are due to the presence of anhydrides and lactide. Pure sarcolactic acid as a preparation does not exist, it is always mixed with these anhydrides, and therefore its specific rotatory power, which is probably to the right, cannot be accurately determined.

Polarising Phenomena of Sarcolactate of Zinc.

The solution of zinc sarcolactate turns the plane of polarised light to the left -7.7° . The turning energy is smaller in the over-saturated than in the normal solutions.

The polarising faculties of sarcolactic acid, its hydrate, zinc salt, and anhydride, may be described as follows:—

Turning farthest to the <i>right</i> ,	. . .	$C_3H_6O_3$
Turning less far to the <i>right</i> ,	. . .	$C_3H_6O_3 + H_2O$
Turning least to the <i>left</i> ,	. . .	$2(C_3H_5O_3)Zn$
Turning more to the <i>left</i> ,	. . .	$2(C_3H_5O_3)Zn + 2H_2O$
Turning farthest to the <i>left</i> ,	. . .	$C_6H_{10}O_5$

Decomposition of Sarcolactic by Sulphuric Acid.

When sarcolactic acid (5 parts) is mixed with water (6 parts) and sulphuric acid (2 parts), and heated in a sealed tube during eight hours to between 140° and 150° , formic acid and acetaldehyde are formed, just as in the case of zymolactic acid. The same decomposition with the addition of acetic acid is obtained by oxydation with potassic dichromate and sulphuric acid. Malonic and oxalic acid are not formed. From this it follows that the constitution of sarcolactic acid is more like that of zymolactic acid than has hitherto been believed when the alleged formation of malonic acid from the former, not given by the latter, mainly guided the considerations of the theorists. The two lactic acids seem of identical structure chemically; but although their atoms are attached to each other by the same ties,

the position of the atoms to each other, or of some of them, is changed. The two acids are isomers *geometrically*, as the four lactic acids are isomers *chemically*.

Physiological and Pathological Indications.

The muscular and nervous system are constantly pervaded by a certain small quantity of lactic acid. This is most probably formed in the tissues themselves as the result of their vital chemism, but in part it may also be carried there, and deposited by the blood. In this latter case the acid, if not ingested with the food as such, may have been formed in the stomach and intestines by fermentative action upon their amylaceous and saccharine contents; it is not probable that lactic acid is a normal ingredient of the gastric juice, or of any of the intestinal juices as they come from the secreting apparatuses. The quantity of lactic acid in brain and muscles increases with continued action, and decreases by rest. It is not impossible that, in the muscles at least, the increase in the acid reaction supposed to be caused by strong activity is due to the presence of some free lactic acid. If this be negatived, as by some it is, the increased amount of lactic acid must be present as lactate. This idea has so far enticed Preyer as to cause him to make experiments on the somniferous action of lactates, and he finds that when they are injected under the skin of animals, and external excitement is kept away, (!) the animals go to sleep. Amongst the various theories of sleep this is perhaps the one which is most crudely chemical, just as the hypotheses which oppose each other, of sleep being due to a congestion of blood to the brain, and of its being due to an absence of blood from the brain, are the most crudely mechanical.

In trichiniasis, where hundreds of thousands of muscular fibres are rapidly destroyed, great masses of decomposition products are necessarily thrown into the blood, and with them no doubt large quantities of lactic acid. Of these a small portion may probably appear in the urine, as we are assured by Simon and Wibel that they have found. In phosphorus poisoning there is a similar destruction of tissue, although it is less pronounced in the muscular system, and appears more prominent in the liver and nervous system. In this toxic disease also large quantities of lactic acid are found in the urine, sufficient to admit of crystallisation of a salt and of its analysis. The modification of lactic acid met with in the urine in both cases is the sarcolactic.

There are two other important diseases in which lactic acid supposed to take an important share—rhabdomyositis of children, and osteomalacia of adults. That lactic acid can be found in the bones of rhabdomyositic children I have myself proved by experiment after it had repeatedly been found by former inquirers.

acid is present in the urine of rachitic children, and sometimes in considerable quantity, was shown by Scherer ("Untersuch. z. Pathol." p. 74) and Marchand ("Physiol. Chemie." p. 105), and Lehmann noticed it in the urine in the osteomalacia of adults. We are now also informed that sarcolactic acid is found in great quantity in some kinds of ovarian cysts, and the uncrystallisable, unpurifiable, ethyleno-lactic acid of Wislicenus this author has himself met with in pathological exudations. We may therefore still summarise the physiological and pathological indications of lactic acid in the urine, in the words of Lehmann ("Physiol. Chem." Cavend. Soc. Ed. 1, 92): *In all cases where the supply of lactates to the blood is very great,—whether this depends on an excess of acid being formed in the muscles, or on the use of a diet tending to produce it, or an imperfect process of oxidation in the blood,—lactic acid may be detected in the urine.* Hence in the urine of the same individual, lactic acid may on one day be present, and on another absent. In the urine of many persons no lactic acid can be detected; and in the urine of others again (especially of persons who, in consequence of repeated catarrhs, suffer from partial relaxation of the pulmonary tissue), it is constantly present. Stall-fed animals, living on amylaceous fodder, excrete lactic acid by the kidneys, while under other conditions this acid cannot be detected in their urine. In most febrile diseases lactic acid may be recognised in the urine.

The position at which we have thus arrived calls more than ever for a thoroughly scientific examination of the chemistry of rheumatic fever, and of the heart disease which so frequently follows in its train. The experiments in what I may call synthetical pathology, of John Simon, and later those of Richardson, have established apparently *prima facie* that lactic acid has an important share in the production of some of the most obvious phenomena of that important disease. It is not necessary to consider it as the only disease produced, or disease-producing matter in what is necessarily a complicated process, but its closer study will necessarily lead to further important information, even if it should prove to have an action analogous only to, and not identical with, the leading features of the rheumatic process. Such inquiries must therefore cover the largest possible ground in order to take in the whole of the chemical phenomena. Thus the examination of urine for lactic acid should be united with that for oxalic acid, as the visible occurrence of the calcium salt of the latter acid has been known to be frequently associated with the presence of at least unusual quantities of lactic acid.

CHAPTER LIII.

DINITROGENISED DERIVATE OF SARCOLACTIC ACID, $C_3H_8N_2O$.

HISTORY, LITERATURE, AND OCCURRENCE.

THIS substance was discovered by Baumstark ("Ann. Chem." 173 (1874), 342). It occurs in normal human urine, but only in small quantity, so that forty litres are required to yield sufficient material for proving its presence. But it occurs in greatly increased quantities in some kinds of disease, which require to be further investigated. The urine of a female who suffered from fatty degeneration of the liver, accompanied with intense jaundice, yielded during five days as much as 4 grm. of the substance. On the other hand, the urine from a series of cases of jaundice yielded none. In the urine of healthy dogs the substance does not occur, and cannot apparently be made to appear by any particular kind of diet. But in the urine of a dog, which had benzoic acid given to it in the food, the new substance appeared during a few days, so that the excretion of seven days yielded 3 grm., but then disappeared again, without any cause for its appearance or disappearance becoming evident.

Mode of Obtaining.

The urine is evaporated on the water-bath to a thick syrup, and this, while yet warm, is mixed with large quantities of absolute alcohol as long as anything is precipitated. The clear solution is filtered, and its alcohol removed entirely by distillation; the residue is acidified with hydrochloric acid, and the hippuric acid completely extracted by ether. The syrup now remaining is diluted with water, over-saturated with ammonia, and precipitated completely with basic acetate of lead. The filtrate from the lead precipitate is treated with hydrothion to remove lead, and is then again evaporated to a syrup. This soon begins to crystallise if allowed to stand in a moderately warm place. Most of the crystals are ~~used~~, but if any of the new compound be present, there is also ~~seen~~ a ~~small~~ ^{white} deposit at the bottom, or a frothy crystalline ~~deposit~~ of the liquid, or sometimes the deposit

the liquid. These deposits are sometimes best united by placing the syrup in a moist place to cause the urea to diffusesce, and then again to cause it to begin to crystallise in a moderate temperature. The mixture is now treated with as much strong alcohol as may be required to dissolve all the urea to a filterable solution. The residue on the filter is washed with alcohol, again dissolved in boiling water, treated with animal charcoal, and slowly evaporated and allowed to cool. Crystals now appear which are white, and frequently project like hippuric acid, several millimètres from the liquid. The similarity of these crystals to those of hippuric acid is so great that, judged by the mere eye, they will certainly be mistaken for them. The analysis of the crystals dried over sulphuric acid led to the formula $C_3H_5N_2O$.

Physical and Chemical Properties.

The crystals are white prisms several m.m. long. Readily soluble in boiling, little soluble in cold water and in spirit, insoluble in absolute alcohol and in ether. They are not changed by being heated up to 250° . The crystals dried over sulphuric acid decrepitate when heated on platinum foil, and then evolve white thick vapours as if the substance was sublimated. On being heated quickly and strongly the crystals fuse and burn, and a smell of burning horn, like that given out by so many nitrogenised substances, is evolved. Heated in a tube the substance fuses, and does not give a sublimate; it then becomes brown and emits a gas smelling of ethylamine. The same gas is evolved when the substance is heated with soda lime. The body is neutral towards litmus, does not enter into combination with bases, but with acids forms compounds which crystallise with difficulty and diffusesce in the air. The substance is precipitated by mercuric nitrate.

The hydrochlorate solution cannot be evaporated at a higher temperature, as it is decomposed and becomes brown. Evaporated in vacuo over burnt lime and sulphuric acid it forms a crystalline mass of salt, which after two recrystallisations from a little alcohol over sulphuric acid has the formula $C_3H_5N_2OHCl$.

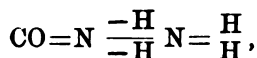
The crystals when treated with nitrous acid while suspended in water give out gas, and the fluid becomes warm. When the action has been completed the liquid is neutralised with soda, evaporated nearly to dryness, made strongly acid with sulphuric acid, and extracted with ether. The residue from the ether extract is an acid, which combines with zinc carbonate; the zinc salt repeatedly crystallised from spirit gives crystallised zinc lactate, containing 23.1 per cent. Zn. and 12.6 per cent. water.

On treatment with concentrated hydriodic acid the salt gives no β -iodopropionic acid. On being boiled the solution of the

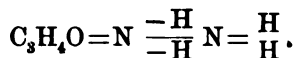
salt decomposes, depositing zinc oxyde. The salt effloresces on drying, and is very easily soluble in water and spirit. These data prove that the lactic acid obtained is the sarcolactic, or lactic acid from flesh, and not the zymolactic or lactic acid from fermentation.

When the new body is boiled with saturated baryta water during several hours, it is decomposed, ammonia, carbonic acid, and a gas smelling like ethylene being evolved. In this reaction one amide is probably expelled first, with formation of an amido-acid. The latter by heating in a sealed tube with baryta to 150° for some time yields ethylamine.

The substance might, from the formula and the decomposition with nitrous acid, have been considered as the diamido-sarcolactic acid $C_3H_4(NH_2)_2O$. But the diamides of the two lactic acids which Baumstark compared had different properties. The new compound has, however, great analogy to the ordinary urea, on the supposition that in this, as in the new compound, the two nitrogen atoms have a different function and dynamicity each. On this hypothesis urea would have the structure formula—



and the new derivate of paralactic acid would be—



It will be seen that the atom of nitrogen on the left is pentadynamic, that on the right tridynamic, in each formula. We are promised further investigation of these highly interesting relations.

CHAPTER LIV

CYSTINE, $C_2H_5NSO_3$

HISTORY AND LITERATURE

CYSTINE was discovered and named by Wollaston ("Phil. Trans." 1810, 223) as the principal constituent of a rare form of urinary calculus. It was analysed by Prout, and by Lassaigne ("Ann. Chim." 23, 328), but both missed the sulphur contained in it. This was found by Baudrimont and Malaguti ("Journ. d. Pharm." 24, 633). Its composition was ascertained by Thaulow ("Ann. Chem." 27, 197).

Occurrence.

Cystine is the principal constituent of a rare description of calculus; small calculi are sometimes made up of pure cystine, and then appear yellow, transparent, wax-like, of a crystalline texture. They cut like dry walnut, may be powdered, and are gritty between the teeth, tasteless, and neutral. When the calculi are not made up of pure cystine, they generally contain an admixture of earthy phosphates, and then are greenish-blue, dirty greenish-grey, or fawn-brown. The calculi which occur in man, but have also been found in dogs (Heller, "Archiv," 6, 458), are most commonly formed in the bladder. But they have also been found in the kidneys, sometimes filling the entire calyces. Cystine is met with in the urine in solution and as a deposit. Where it occurs dissolved it is probably by means of some alkali, either the alkali by means of which it was excreted from the kidneys, or an alkali formed in the urinary passages, ammonia which has lost some carbonic acid, as is usual in decomposed urine. Scherer (Virchow's "Archiv." 10, 228) believed that he had found cystine in the liver of typhus patients. Cloëtta once obtained it from the kidneys of oxen, but could not meet with it again in the same substance.

Mode of Obtaining Pure.

The cystine calculus is powdered, dissolved in caustic potash, and precipitated by acetic acid. By repetition of this process and the following all phosphates are removed. Uric acid is

excluded by dissolving the cystine alternately in caustic ammonia and in hydrochloric acid, wherein uric acid is almost insoluble, cystine soluble. Lastly, it is crystallised from caustic ammonia.

Physical and Chemical Properties.

The number of hydrogen atoms are variously given as 7 by Gmelin, 6 by Thaulow based on analysis, and 5 by Dewar and Gamgee based on speculation.

Cystine crystallises in six-sided plates. These crystals are very characteristic, and a valuable means of diagnosis by the aid of the microscope. It is insoluble in water, but soluble in dilute mineral acids, from which solution it is precipitated by ammoniac carbonate. The solutions in acids mostly yield the relative salts on evaporation in a crystallised state. The phosphate forms tufts of needles; so does the sulphate. A solution of cystine in dilute sulphuric acid turns brown when strongly heated (Robert, "Journ. Pharm." 7, 165). Oil of vitriol saturated with cystine yields a colourless, viscid, non-crystallisable mass, which is soluble in water, and after drying in vacuo over oil of vitriol contains 10.4 per cent. of sulphuric acid. This is probably a mixture of a sulphate with much free cystine. The hydrochlorate crystallises in needles, which give off hydrochloric acid at 100°. They are nearly insoluble in water. Hydrochloric acid saturated as completely as possible with cystine still reddens litmus. The pearly needles which this solution yields on spontaneous evaporation are permanent in the air, and contain, after being dried in the sun, 5.3 per cent. HCl. This salt, like the sulphate, must contain much free cystine. The nitrate crystals were found to contain only 3.1 per cent. of HNO_3 . The basic properties of cystine are therefore very feeble. It may also form compounds in which it takes the place of an acid. Of such compounds Pelouze (Note appended to Civiale's "Mémoire sur les Calculs de Cystine," in Civiale's "Du Traitement Médical de la Pierre") described two with silver, which he termed cystates. It is probable that cystine is an amido-acid, and that its nitrogen can be expelled, and its acid nucleus be transformed into an oxyacid by treatment with nitrous acid.

Cystine is easily soluble in a watery solution of ammonia, potash, soda, and lime; also in the bicarbonates of potassium and sodium, but not in bicarbonate of ammonium. The solution in ammonia on spontaneous evaporation leaves the cystine pure in crystals. The other solutions leave granular crystals, the composition of which is not ascertained. From the alkaline solutions, cystine is precipitated, after a few seconds, by acetic, tartaric, and citric acids, in the form of a fine white powder; these solutions are, however, not precipitated by either sulphuric,

hydrochloric, or nitric acid. Cystine is soluble in a water solution of oxalic acid.

When subjected to dry distillation, cystine yields prussic acid, carbonate of ammonium, a fluid, thick and stinking oil, and leaves a spongy charcoal. Heated in the open air, it develops sulphurous acid, recognisable by the smell, but does not fuse, or melt, or blister. When fused with caustic potash, it gives off an inflammable gas, which burns with a flame similar to that of sulphide of carbon, and evolves sulphurous acid. When cystine is boiled in caustic potash solution, in which some hydrated oxide of lead has previously been dissolved, a large precipitate of sulphuret of lead is obtained. The solution of cystine in excess of nitric acid, on evaporation by boiling, leaves at first a white, not transparent mass, which becomes brown and black, and contains sulphuric acid.

When a little cystine or a piece of a calculus is dissolved in a small quantity of caustic potash with the aid of heat—the solution after cooling is diluted with water, and then some solution of nitro-prusside of sodium added, a violet colour is produced, (Müller, "Arch. Pharm." (3) 1, 308, and "Chem. Centr. Bl." (1872), 775).

When treated with hydrochloric acid and zinc, or tin, cystine evolves hydrothion easily recognised by the smell and the blackening of paper drenched with lead acetate. An ammoniacal solution of cystine gives no apparent reaction in the cold with an ammoniacal solution of argentic nitrate; but when to the mixture nitric acid is added in excess, a canary yellow precipitate ensues, which seems to be a compound of argentic nitrate with cystine. The filtrate blackens on the application of heat. If the mixed ammoniacal solutions of cystine and argentic nitrate are heated, argentic sulphide is deposited, but the liquid contains neither sulphuric nor oxalic acid. When cystine is treated under water and with the aid of heat, with nitrous acid, it dissolves: the clear solution contains sulphuric, but no oxalic acid, and reduces silver solution (Dewar and Gangee "Journ. Anat. Physiol." 7, 142).

Cramer "Jahresb." (1865), 654 gave as the formula for cystine $C_2H_3(SH)(NH_2)CO_2H$. The authors just mentioned suppose that if this formula were correct, cystine ought not, on oxydation, to yield, as is often assumed, glyceric acid, but a sulpho-acid, probably amido-sulpho-pyrotartaric acid.

Peculiarities of Cystiniferous Urine.

Müller ("Archiv. der Pharm." (1852, März) 228) was the first to find cystine dissolved in the alkaline urine of a boy six and a half years old. Here the alkaline condition seemed to be due to the presence of a large cystine calculus in the bladder. After

the operation of lithotomy, the urine became acid. Two months later the urine became again alkaline, and gave a deposit which, when cleared of earthy phosphates by means of acetic acid, showed itself to be cystine again. The urine, on being filtered and treated with acetic acid, after the lapse of twenty-four hours, yielded another precipitate of cystine.

Urine depositing cystine is generally turbid when voided, either because it is ammoniacal, or because the cystine deposit is already formed. The deposit does not, to the naked eye, differ much from one of fawn-coloured urates. The urine in which it forms is usually faintly acid, and when made more acid by acetic acid deposits a further quantity of cystine. A cystine deposit is characterised by its not dissolving on the application of heat, and by its ready solubility in caustic ammonia. Urine which contains cystine is said to evolve sulphide of ammonium during its alkaline decomposition.

In the case of cystinuria described by Löbisch ("Ann. Chem." 182 (1876), 231), the acid urine of a young man, weighing 76 kilos., deposited during twenty-four hours after emission a voluminous mass of what appeared under the microscope colourless hexagonal plates. The quantity of cystine contained in the urine was determined by adding to 500 c.c. of it 20 c.c. of acetic acid of 20 per cent. strength, and letting the mixture stand in a cool place. After twenty-four hours a deposit had formed, which consisted of cystine-crystals, uric acid, oxalate of calcium, and sometimes of urates. The deposit was placed upon a filter, washed with dilute acetic acid and hot water, dried, and weighed. The weighed filter and contents were then placed upon a funnel, treated with some dilute hydrochloric acid, washed, and dried. The loss by the hydrochloric acid treatment was calculated as cystine. The proceeding was controlled by dissolving a known quantity of cystine in healthy urine, and precipitating it in the manner described: 96.6 per cent. of it were recovered.

The urine when voided was perfectly clear, had a healthy yellow colour, was always acid (one day excepted, when it was alkaline in consequence of the patient's taking vegetable food exclusively), and never had any peculiar smell not presented by ordinary urine. The deposition of cystine began in from ten to twelve hours after evacuation, and the deposit was at first in the form of minute loose grains much like oxalate of calcium.

The urine was examined on fourteen days, and quantity, specific gravity, urea, uric acid, cystine, and sulphuric acid were quantitatively estimated. The means of the days 1 to 6, and 11 to 14 (the days 7 to 10 being excluded because influenced by peculiar vegetable diet) were urea, =33.28 grm.; uric acid, =0.5445 grm.; cystine, =0.3930 grm.; sulphuric acid, 2.4390 grm.; total quantity of urine, 1296 c.c.

The excretion of cystine therefore did not interfere noticeably with the quantities of the normal constituents. The amount of nitrogen excreted in the cystine was only 0.045 out of a total of 15.757 grm., of which 15.530 were in urea and 0.182 in uric acid. The urine is said to have yielded biliary acid, recognised by Pettenkofer's test in the product from the lead and ammonia precipitate from only 300 c.c.

Toel ("Ann. Chem." 96, 247) determined the cystine excreted by each of two sisters affected with cystinuria to be 1.4 grm. in twenty-four hours. Pletzer ("Archiv. d. Vereins f. gem. Arb." 3, 162), in the same cases as those examined by Toel, found the crystals of cystine smallest when the urine was acid, largest when it was alkaline. The amount of cystine was said to have been increased by a diet of fish and leguminous vegetables. Organic acids lessened the amount. In Toel's analysis it was assumed that all sulphur which was not precipitated by baryta in acid solution, and could only be obtained as sulphuric acid after oxydation of the residue of the urine, was present in the form of cystine. This is obviously unproved, and to make Toel's figures more correct it would be necessary to subtract from them an average amount of sulphur present in the unknown form. If this unknown form should ultimately prove to be cystine, the operation would still be necessary to show the excess over the normal quantity.

Cystinuria often, relatively to the total number of cases observed, occurs in several members of the same family, as is shown by the observations of Prout, Marcet, Civiale, Lenoir, Shearman, Bird, and Toel. Marcet relates the cases of two brothers, in whose kidneys cystine calculi were found. Both Lenoir and Civiale extracted cystine calculi from the bladders of two brothers. Toel and Peltz observed two sisters who were subject to continual cystinuria and occasionally discharged small concretions. Prout supposed that there was a hereditary disposition to it, but this hypothesis is not supported by any positive observations.

Cystinuria occurs more frequently in children and young adults than in persons of advanced age. It does not seem connected with any particular dyscrasia, such as tuberculous or scrophulous disease; the view once supported by Shearman, that struma and chlorosis were often combined with it has been combated by Fabre ("De la Cystine," Thèse, Paris, 1839). In a young woman, from whom Jordan extracted a cystine calculus some years ago in the Manchester Infirmary, Roberts found considerable tuberculous consolidation of both apices.

Persons may suffer from cystinuria without showing any other objective symptoms except those caused by physical irritation of the concretions which may form in the kidneys or the bladder, and

by their passage through the urinary canals if they are small. Two brothers who were operated by Civiale for large cystine calculi were known to have been excreting cystine in quantity for six years continuously, without any deterioration of their health having been perceptible. The sisters observed by Peltz and Toel were healthy, but suffered occasionally from the passage of small renal concretions.

Cystine Calculi.

In urinary calculi cystine presents the appearance of a yellowish, shining, confusedly crystalline mass; or it consists of wax-yellow, translucent, elongated square octohedrons. (Schindler, "Mag. Pharm." 29, 264). It crackles between the teeth, is tasteless, neutral, easily rubbed to a powder. The calculus observed by Wollaston contained 97·5 per cent. of cystine, and 2·5 per cent. of calcic phosphate; its sp. gr. was 1·577. A calculus observed by Taylor ("Phil. Mag." 12, 337) contained 91 per cent. of cystine, and had 1·13 sp. gr.; a pure cystine calculus observed by Venables ("N. Quart. Journ. of Sc." 7, 30) had 1·7143 sp. gr. Sometimes cystine calculi have a nucleus of uric acid. In a specimen in the Museum of the Manchester Infirmary, described and figured by Roberts (l. c., p. 218), the central nodule is uric acid, around this is a body of pure cystine, overlying this layer of mixed uric acid and cystine, and enveloping the whole a crust of mixed phosphates and cystine.

Cystine calculi, when exposed long to daylight, assume a pale green colour, probably from a change in a colouring matter by which they are penetrated. Roberts relates of the calculus just referred to, that it had been divided equatorially—one-half lay in the cabinet with its cut surface downwards, and the other half was with the cut surface upwards, exposed to the light. The latter had a delicate emerald green tint, while the former preserved its original yellow colour.

Cystine calculi, owing to their friability and softness, are favourable objects for operation by lithotrixy. Out of 129 calculi, 2 were found to consist of cystine (Taylor).

CHAPTER LV.

ALCOHOL, C_2H_6O .

INTRODUCTION.

PERHAPS alcohol was known to the ancients, and the famous Pramnic wine of which Homer speaks, and which was yet powerful enough to inebriate when diluted with twenty measures of water, contained or was a distilled spirit. But although poetry may have been, science did not actually become, acquainted with alcohol in its distinct and isolated form before the 12th century, when it was endowed with the name which it at present bears, and which signifies "the spirit," by its supposed first discoverer, the Arabian physician Geber. The rest of the chemistry of alcohol is mainly a product of the present century.

Occurrence.

Alcohol is the principal produce of the fermentation of the juice of the grape, and no doubt it was by the natural transformation of the juice of the grape that alcohol was first discovered. Other fruits containing sugar also yield alcohol by the natural decomposition which they undergo after they are taken from the tree and crushed. Alcohol, then, is the active ingredient of all vinous or spirituous liquids, including those obtained from grain by the processes of malting and fermenting. It is directly derived from a kind of sugar, which from its aptitude to decompose into alcohol and carbonic acid under the influence of yeast may appropriately be designated as *fermentescible sugar*, and about which more will be found under the chapter relating to diabetic or grape sugar.

Other sugars, mannite, dulcite, sorbine, lactose, including glycerine, cane sugar, starch, gum, and the dextrine which is found in the liver, or so-called hepatine, yield small quantities of alcohol under certain influences, *e.g.*, water, chalk, and cheese, at a temperature not exceeding 60° . Alcohol can also be prepared synthetically in the laboratory by combining carbon and hydrogen under the influence of the electric discharge of a powerful battery to acetylene, C_2H_4 , dissolving this gas in sulphuric acid, mixing the solution with water, and distilling it.

Mode of Obtaining Pure.

Alcohol is separated from the liquids in which it has been produced by fermentation, by means of evaporation and condensation in a confined space, a process which is termed distillation. As the alcohol from watery liquids is generally mixed with much water, and other impurities, it has to be made more spirituous and pure by a process termed rectification. In the most perfect modern kinds of apparatus for the production of alcohol these operations are all performed at one and the same time, and a highly concentrated pure spirit is at once obtained. But by distillation alone alcohol free from water, or as it is termed absolute alcohol, cannot be obtained. To extract the last portions of water from spirit it is necessary to treat it with substances having greater affinity for water than itself, such as freshly burnt lime.

Physical and Chemical Properties of Absolute Alcohol.

Absolute alcohol is a liquid. It is colourless, has an agreeable flavour, and burns when fire is set to it. It has also a burning taste, but the taste of pure alcohol is very agreeable indeed, and this is quite the reverse of what is sometimes said, namely, that distilled alcohol has a nasty taste. It has a nasty taste, as ordinarily obtained, but this is due to the circumstance that certain products of decomposition are mixed with it, which, however, can be entirely removed, as Döbereiner has shown, by passing the distilled alcohol 50 times over animal charcoal. When it passes 50 times it is absolutely pure, and has the chemical properties and taste described.

Its specific gravity at zero is 0.8095. At 14, however, which is the ordinary temperature, it is 0.7982. It boils at 78 of the centigrade thermometer, under the pressure of 760 millimètres of the barometer. Even at the strongest cold, a temperature of -100° , it is only transformed into a thick fluid, but it is not solidified at any temperature or by any means. It can be burnt in a spirit lamp, and there comes little or no light from it. Alcohol attracts the moisture very rapidly, so that it may be compared to sulphuric acid in its power of so doing. With water it becomes warm and then contracts; 49.8 volumes of water, and 53.7 volumes of alcohol, which if they mixed without contraction would give 103.5, will contract so as to form 100.

Alcohol may be considered as the hydroxyl compound of a radical ethyl, C_2H_5HO ; or if ethyl be considered as a compound radicle, alcohol may be said to consist of three primary compound radicles, CH_2CH_3HO .

Mode of Determining the Quantity of Alcohol contained in Watery Solutions of Different Strengths.

This is best done by determining the specific gravity of the

mixture. This operation can be carried out in two ways, by the balance and by the gravimeter. For the purpose of determinations such as occur in the practice of medicine or in experimental pathology, the gravimeter can but seldom be used. More frequently will it be possible to determine the specific gravity of distillates by the balance. But even this method is not available for the small quantities which occur in observations in individual cases. In these cases it is necessary to transform the alcohol to be determined into acetic acid, and to determine this product of transformation by an acidimetric volumetric method to be described.

Note on the Definition of "Proof Spirit."

By an Act of Parliament which was passed in the 56th year of the reign of George III., chapter 160, in the year 1816, it is enacted that the standard of all spirits upon which the excise shall levy taxes is to be a mixture of alcohol and water which shall weigh 12, while the same volume of distilled water shall weigh 13, all at a temperature of 51° Fahr.; or in the words of the Act: "And whereas since the passing of the said Acts an hydrometer called Sykes's hydrometer has with great care been completed, and has, by proper experiments made for that purpose, been ascertained to denote as proof-spirit that which at the temperature of 51 degrees by Fahrenheit's thermometer weighs exactly $\frac{17}{13}$ parts of an equal measure of distilled water." This curious standard is supposed to have been obtained as follows:—Before science had anything to do with buying and selling, it was usual to take a saucer and put a little gunpowder in it, and then pour a little of the spirit which was to be tested over it. Then the spirit was set fire to and burned, and at the conclusion of the combustion it was observed whether or not and to what extent the gunpowder also took fire. The spirit was called "proof" if it was sufficiently concentrated to cause the gunpowder to burn; for if the spirit contained so much water that at the end of the combustion the gunpowder was wet, then of course it did not burn. This, then, is the derivation of "proof spirit," and according to this standard nearly all the spirit used in this country is now bought and sold. Doubtless we shall in time conform to the method of other countries, so that also here a spirit shall be bought and sold according to its percentage by weight in volume.

Mode of Isolating Alcohol from Organic Liquids.

This method applies more particularly to urine, but also to the water extracts of organs, to blood and lymph, and serous effusions. From the albuminous fluids the albumen will have to be removed before boiling by treatment with heat in a closed

vessel, and filtration after cooling. We put the liquid to be tested into a retort, and add a small quantity of tannic acid to prevent frothing. If we were to boil urine merely by itself, without adding tannic acid, we would probably have bumping and frothing, and a small quantity of urine would pass over into the condenser, and we would lose our distillation. Having thus distilled the fluid once by itself, we proceed to redistil it in order to remove from it any acid that may be present. We add a small quantity of caustic potash to the liquid, and after having given time for the reaction we proceed to distil it again. The effect of that process is that all the volatile acids are retained, while nothing but the alcohol and the ether present passes over. We have now already reduced the quantity of the fluid very much, and subject it now to a third distillation, this time with sulphuric acid, so that any volatile alkalies which may have been driven out in the first instance may not pass over but be retained. The third distillate, then, which is mostly only about one-eighth part of the original quantity, contains all the alcohol, no volatile acids, no volatile alkalies, and is the liquid which we use for the test to be described.

Chromic Acid Test for Alcohol.

Alcohol when it is brought in contact with free chromic acid is so much heated that it takes fire, and a kind of explosion takes place; but when it is mixed with a dilute solution of chromic acid, such as is produced by mixing dichromate of potash with sulphuric acid, we only obtain a still reduction, indicated by a transformation of the red colour of our test into a green colour. The sulphate of oxyde of chromium is formed from the chromic acid. We generally take one part of the dichromate to 300 of the sulphuric acid. We must take care to mix the distillate with two parts of sulphuric acid in the concentrated state, so that for the test we have considerably concentrated liquids. If we have not concentrated liquids we are liable to miss our test. If we pour a little of this into the mixture so that it sinks to the bottom, we perceive that where the one fluid touches the other there is a deep green colour, and then a ring of lighter green; and even if we have as little as one-fourth or one-tenth of a grain of alcohol in half an ounce of water, it will yet, by means of this test, be indicated. The test, therefore, is a very delicate one. Of course it is necessary that we should, before applying this test, have taken the precaution of distilling the fluid three times, as above detailed, otherwise the test will be fallacious on account of the organic matters not being alcohol decomposing the chromic acid in the same manner as alcohol.

The particulars of proceeding for determining alcohol in urine are the following:—Test liquid: 1 part of dichromate of potash

dissolved in 300 parts of sulphuric acid, that is, the solution which has already been described. If we make the reaction very nicely we can even discover the one-hundredth part of a grain of alcohol, but not in the quantity of half an ounce of fluid. Applied to the urine we need not generally take more than two ounces of urine. It is necessary that we should save labour as much as possible in these operations, which have, in long researches, to be often repeated, and therefore it is well to know that two ounces will be a sufficient quantity to treat. Of that we distil off one-third under the precaution which I have mentioned as to tannic acid. Then of the distillate we draw off again one-third, so that we have one-sixth of the original; and of that again one-third, so that we have one-ninth of the original. During the operation of distillation, if we want to make quantitative researches it is necessary that we should close the whole of our apparatus so that it be air-tight, and we should provide the receiver with a mercurial valve.

Normal urine when tested gives no reaction for alcohol under any circumstances unless alcohol has previously been taken. If we add one-tenth grain of absolute alcohol to two ounces of urine, and afterwards distil, we get a reaction very distinctly, which shows the great delicacy of the test. Only one source of fallacy exists with regard to it, and that is, that a small quantity of ether of some kind or other may be present, and that ether would, of course, in the process which we shall have to consider presently, be decomposed, and also be transformed into acetic acid and increase it. It is possible, for example, that after the drinking of Greek wines, which contain much aldehyde, a quantity of this latter escapes by the urine.

Mode of Estimating Small Quantities of Alcohol by Transformation into Acetic Acid and Acidimetric Volumetric Determination (Dupré's Method).

We have a quantity of alcohol obtained from urine, and we want to determine how much it is. The tenth of a grain of alcohol in two ounces of water would not admit of any specific gravity determination. It would not be possible to immerse any instrument, or to put that small quantity on a balance sufficiently fine to determine that, and therefore it is necessary to take a somewhat circuitous but still a quite certain route, and that is, we take the distillates and oxydise the alcohol therein contained to acetic acid, and determine it by quantitative analysis, or even make a salt of it. Alcohol does not combine with any other body; we cannot increase its weight; we cannot retain it in any way; whereas acetic acid combines with many,

owing to this property the quantity of the acid can be very determined, even in solutions. This is done in the

following way:—We enclose the distillate with a certain quantity of the dichromate and sulphuric acid mixture in a flask, close it air-tight with a caoutchouc stopper, and tie it down well by means of wire. This bottle we now heat for two hours in a water-bath at a certain temperature, never amounting to boiling. During that time the whole of the alcohol is transformed into acetic acid. We have to distil that over, and for that purpose it is only necessary to distil the mixture down to one-half. We now determine the acidity of our distillate by applying to it a caustic soda solution of which we know the strength, and so ascertain the amount of acetic acid contained in the distillate. According to this plan the following experiments were made. The experiments on the large scale mentioned above were not so made, but resulted in the isolation of the pure absolute alcohol.

Physiological Effects of Alcohol Measured by Renal Elimination.

Some years ago there was a great discussion on the question: Is alcohol food or physic? while hundreds of men talked about it, none ever dreamed of setting to work to ascertain the solution of the question, until three French learned men, namely, Lallemand, Perrin, and Duroy (the first one the late surgeon who died in the French Mexican expedition), investigated the question whether alcohol when it was taken into the body was actually burned up, as Liebig had stated, or whether it was given out again unchanged. They caused a man who could consume a great quantity of alcohol to drink a certain quantity, and then they collected his urine, distilled it over, and to their very great surprise they found that the alcohol reappeared in the urine. They could burn it, they could show its presence, and they straightway went to the conclusion that the alcohol is entirely secreted, and is a stimulant and not a food. In 1865 this question engaged my attention, and I availed myself of an opportunity which I had of making an experiment on a large scale. 44 bottles of wine were drunk by 33 men during six hours of athletic sports, and their urine passed during six hours was collected under my observation for analysis. It was then subjected to 24 distillations, whereby with the aid of dehydration by copper sulphate a small quantity of alcohol was obtained weighing 10 gm. Then arose the question: In what proportion does the alcohol recovered stand to the alcohol consumed? and there we must again be guided by chemical analysis. The 44 bottles which were drunk by the 33 men contained 4000 gm. of absolute alcohol, and there were, after dehydration, 10 gm. of alcohol obtained, the rest having been burned up in the system. Supposing that 10 gm. more passed out through the

breath, the pores of the skin, &c., it would only give 5 grm. out of every thousand, or $\frac{1}{2}$ per cent., as the quantity which was left unused by the system. We have, therefore, here a direct proof that out of the whole quantity of alcohol drank only a quarter per cent. was excreted by the kidneys.

Subsequently Dr. Dupré, Lecturer on Chemistry to the Westminster Hospital, made a great many smaller experiments in order to test whether the above was not an exceptional fact but the actual and invariable rule.

Experiment with Bordeaux Wine upon Six Men.—Six young men consumed 255 fluid oz. of red Bordeaux wine, containing 11,018 grains of absolute alcohol. The observation commenced at 1 o'clock P.M., and within an hour and a half, during which the men were engaged in sports and gymnastic exercises, four-fifths of the wine had been taken. All were more or less affected, two very strongly, which had not been the case in the previous experiment. Their urine was collected till 5 P.M., and found to amount to 216 fluid oz. It was four times distilled with the usual precautions. The final distillate amounted to 3 oz. The specific gravity of this distillate at 15.5° C. was 989.16, and therefore contained 6.32 per cent. of absolute alcohol by weight. A portion of the same distillate, when oxydised by potassium dichromate and sulphuric acid, gave an amount of acetic acid which was equivalent to 6 per cent. alcohol. Another portion of the distillate tested in Geissler's vaporimeter gave an indication leading to 7.3 per cent. alcohol, which would indicate that there was a small quantity of a substance more volatile than alcohol contained in the mixture.

Absolute alcohol taken in 255 oz. of wine = 11,088 grains.

" " obtained from 216 oz. of urine = 91.03 grains.

Therefore of every 121.8 grains of alcohol taken, 1 grain was reobtained from the urine. Of 100 absolute alcohol only 0.82, or a little more than four-fifths per cent., was recovered.

In my experiment on the large scale we could not be sure whether some very small quantity of the wine may not have been accidentally lost. But the foregoing experiment was minutely accurate in this respect. The quicker consumption in the second case may have made a difference, for less alcohol passes into the urine in proportion as we drink it in smaller quantities and at longer intervals; and I believe from further experiments that there is a limit, and that if we do not pass that limit no alcohol whatsoever, excepting the merest infinitesimal portion, passes into the urine, and that is 8, or 10, or 12 ounces of wine, namely, just that quantity which a reasonable man might drink with advantage.

Estimation of the Alcohol Eliminated by the Kidneys in Healthy Individuals, after the Ingestion into the Stomach of different Alcoholic Liquids containing known quantities of Absolute Alcohol (Dupré).

Experiments with Rhine Wine upon a Man.—The subject of the experiment voided all urine at 10.30 A.M., and took 10 oz. of Rhine wine containing 1 oz. by measure of absolute alcohol. While the urine passed at 10.30 had yielded no tests indicating the presence of alcohol,

At 11.30 A.M.	2 oz.	of urine passed contained alcohol.	
At 12.30 P.M.	1½ oz.	do.	do.
At 1.30 P.M.	1½ oz.	"	} contained no alcohol.
At 2.30 P.M.	1 oz.	"	
At 3.30 P.M.	1½ oz.	"	
At 4.30 P.M.	1½ oz.	"	
At 5.30 P.M.	3 oz.	(2 oz. distilled)	

The urine from 5.30 P.M. to 9.30 A.M. of the next day, 13 oz. in all, was distilled repeatedly until it amounted at last to ¼ oz.; it contained no alcohol.

When the reactions which were yielded by the urine which contained alcohol were compared to those of fluids containing a known amount of alcohol, it was estimated that less than $\frac{1}{10}$ (one-tenth) of a grain of alcohol was present in all. In this case, therefore, less than $\frac{1}{10000}$ of the alcohol taken appeared in the urine.

Experiment with Red Bordeaux Wine upon a Man.—The subject emptied his bladder at 11 A.M., and the urine was found to be free from alcohol. He then drank 8 oz. of red Bordeaux wine, containing 1 oz. by measure of absolute alcohol. The urine passed at 12 o'clock (noon) measured 5½ oz. and contained alcohol, but only the slightest trace, less than $\frac{1}{10000}$ of the whole taken. 2½ oz. passed at 1 P.M.; 2 oz. passed at 2; 1 oz. passed at 3; 2 oz. passed at 4 o'clock P.M., were all quite free from alcohol.

Experiment with Rum upon a Healthy Man.—The subject emptied the bladder at 11 o'clock P.M., took 2 oz. of rum of almost proof strength, and went to bed half an hour afterwards. All urine passed during 12 hours succeeding was collected, and amounted to 13 oz. After the addition of a little sulphuric acid it was subjected to distillation, and 5 oz. of distillate were obtained. This was made alkaline and again distilled until 1½ oz. of distillate were obtained. This was again made alkaline and 1 oz. of fluid drawn off. Of this last fluid 1 c.c. mixed with the chromic acid test gave only the slightest possible reduction,

and that only after some time. In order to obtain an estimate of some kind of the quantity of alcohol contained in the 1 oz. last distillate, 1 c.c. of absolute alcohol was mixed with 2000 c.c. of water. 1 c.c. of this mixture added to 1 c.c. of chromic acid test gave a strong reduction, and even $\frac{1}{2}$ c.c. gave a slight effect, which became more marked on standing. We may therefore estimate that the last distillate contained less than 1 alcohol in 2000 water, or the 1 oz. less than $\frac{1}{4}$ of a grain. Consequently of the whole of the alcohol consumed less than $\frac{1}{8000}$ part reappeared in the excretion.

Estimation of the Alcohol Eliminated by the Kidneys in Sick Individuals, after the Ingestion into the Stomach of Alcoholic Liquids containing known quantities of Absolute Alcohol.

The question of the analysis of urine in regard to alcohol is of the utmost practical importance in reference to the treatment of fever and acute diseases, in fact any diseases whatever. Of late years the practice has arisen of treating diseases, particularly fevers, with large quantities of alcohol. This practice was mainly introduced by the late Dr. Todd of King's College Hospital. In some cases there 30 and 40 ounces of brandy were consumed by a single patient in twenty-four hours, and, according to the records which were kept, those persons experienced no disadvantage whatever from taking those enormous quantities of alcohol. 20 oz. of absolute alcohol would kill any ordinary healthy person if he drank it in twenty-four hours, but with these fever patients the higher their fever the more alcohol could they consume, and apparently without any disadvantage to themselves, but rather the contrary. Now there came, of course, the question, What becomes of this alcohol? Is it excreted? Is it used merely as chloroform is, only to produce anaesthesia, and does it then go away again or not? and Dupré therefore made the experiment here related.

Experiments with Wine and Brandy upon a case of Typhus Fever.—The patient took 6 oz. of brandy daily, and on some days additional quantities of wine.

First day of experiment.—Total urine from twenty-four hours 20 oz.; distilled with acid, alkali and acid, as in the experiment with rum. 1 oz. of final distillate contained less than $\frac{1}{4}$ gr. of alcohol.

Second day.—6 oz. of brandy and 18 $\frac{1}{2}$ oz. of wine. The last distillate of 1 oz. contained decidedly less than $\frac{1}{2}$, a little more than $\frac{1}{4}$ of a gr. of alcohol.

Third day.—6 oz. of brandy and 15 $\frac{1}{2}$ oz. of wine. The last distillate of 1 oz. contained less than $\frac{1}{4}$ gr. of alcohol.

Fourth day.—6 oz. of brandy only. The final distillate from

620 c.c. of urine, amounting to 1 oz., contained less than $\frac{1}{2}$, a little more than $\frac{1}{4}$ of a grain of alcohol.

Fifth day.—6 oz. of brandy only. The last distillate from 630 c.c. of urine contained less than $\frac{1}{2}$, a little more than $\frac{1}{8}$ of a gr. of absolute alcohol.

Sixth day.—6 oz. of brandy only. The last distillate was oxydised by chromic acid, and the acetic acid produced was estimated; it indicated less than $\frac{1}{2}$ gr. of alcohol.

Seventh day.—6 oz. of brandy. The fæces were examined exactly like the urine, and less than $\frac{1}{8}$ gr. of alcohol found to be present. $\frac{1}{2}$ gr. of alcohol was added to 18 oz. of water and distilled as the urine in the foregoing experiment. The last distillate of 1 oz. contained more than $\frac{1}{2}$, only a little less than $\frac{1}{2}$ gr. of absolute alcohol.

Now we see here the quantities of alcohol which proceed from the typhus body are not larger than those which would pass from an ordinary healthy person; consequently it was quite clear that these enormous quantities of alcohol taken are consumed in the economy, are oxydised. Whether they are beneficially consumed or otherwise must remain for future research to determine; but I have not the slightest doubt, from my own experience, that the giving to typhus patients considerable quantities of wines and alcoholic drinks, not concentrated, but refreshing, stimulating, good, well-tasting drinks, containing not much sugar, is one of the most beneficial things that can be done.

These researches might be multiplied. In fact they ought to be spread over a much larger number of cases.

*Physiological, Pathological, and Social Aspect of the Alcohol
Question as Affecting Kidney Elimination.*

We will now consider, for a short time, the physiological effects of alcohol, in order to make our case complete. It is found that alcohol, when taken in large quantities, before it produces collapse and intoxication, lowers the temperature of the body considerably. Experiments have been made upon drunkards, or at least people who are in the habit of drinking a great deal. If we take such a man, and let him drink as much as he can and likes, we find that his temperature when he is in that state is considerably decreased, even by one or two degrees. In ordinary persons who take the quantity of alcohol which I propose to make the standard, namely, two ounces in a given time, no lowering of the temperature takes place, but rather a slight increase, a quarter of a degree or so, but not more.

A reaction of alcohol which we make use of is its property of attracting water, by means of which it precipitates albumen. When we mix the alcohol with white of egg albumen is precipi-

tated. For a time this precipitate is soluble in water, but after a certain time it is no longer so. The anatomical specimens which we have in our museums are all preserved in that way. The water is withdrawn from them by the alcohol, they are repeatedly steeped, and ultimately they are kept in alcohol almost unchangeable. Alcohol is also made use of for the preservation of many kinds of fruit, such as cherries. It is a very curious fact that the pulp of fruit has a very great power of retaining alcohol, so much so that in the making of wines in France it is very well known that there is much alcohol contained in the mure, or the residue of the stalks, and the husks of black grapes, and that it is necessary to press the mure very strongly in order to obtain the alcohol which is in the mixture of mure and wine. And so when we steep pears, or apricots, or peaches, or any of those many fruits which are preserved in France, we always find that they attract a large quantity of spirit, and the liquid which we press out of the fruit itself is much stronger in respect to alcohol than the liquid in which it is suspended. Thus in eating brandy cherries we eat more concentrated brandy than we would drink if we were to drink the liquid in which they are kept.

I will for a moment consider the large quantities of alcohol which are consumed in this country. In England there are annually consumed 20,000,000 barrels of beer of 36 gallons each. Wine is not comparatively much drunk in this country, but brandy is in enormous quantities. The tax upon alcohol as a whole realises more than £10,000,000 of revenue, and we can see, therefore, that alcohol is drunk by almost the whole of the population, with no very great exception. There is no doubt that by this practice of drinking alcohol in large quantities, particularly what are called "raw spirits," many diseases are engendered, and in London in particular a vast amount of the disease which shows itself in the hospitals is caused by the consumption of enormous quantities of porter on the part of the labouring classes. If we observe labourers at work, in building houses, for example, we sometimes see them throughout the day drinking porter by the half pint or pint, and the potman comes round from the public-house at frequent intervals with fresh supplies; and this independently of what the labourer will drink at the public-house after his work is over. These cases furnish the staple of particular forms of kidney disease; and the habit of drinking large quantities of spirits and beer is to be deprecated as highly dangerous and objectionable. But when from this the conclusion is drawn that alcohol ought altogether to be abandoned, and that we all ought to do without any alcohol, I must say that that is one of the most overstrained propositions that could be made. Alcohol, when we have worked and are fatigued, is a great

restorative and stimulant and food, and one of the greatest necessities of human life; and perhaps there has been no time and no nation in which some kind of alcohol has not been used, and mostly in the largest number of cases beneficially. If we do not exaggerate the quantity which we introduce into our stomach we will never have reason to fear that our kidneys will be damaged by that quantity of alcohol which will pass through them and be excreted.

CHAPTER LVI.

ACETONE, C_3H_6O .

HISTORY AND LITERATURE.

ACETONE was discovered in diabetic urine by Petters ("Vierteljahrsschrift für die Pract. Heilkunde," Prag. 3 (1857), 87), under the guidance and at the suggestion of Lerch, then Director of the Institute for Animal Chemistry at Prague. The researches of Rupstein ("Centralbl. Med. Wissenschaft," 1874, Nr. 55) suggested that the acetone obtained from diabetic urine is not present in it as such, but is the product of the decomposition by boiling of an acid, ethyl-diacetic acid, which on decomposition yields acetone, alcohol, and carbonic acid (Geuther). This view has not been confirmed by the investigations of Markownikoff ("Ann. Chem." 182 (1876), 362), who, although he found some alcohol by the side of the acetone in the urine of diabetic patients, showed that it did not stand in that proportion to the acetone which would be demanded by Rupstein's hypothesis.

Mode of Obtaining Acetone.

Acetone is obtained by the destructive distillation of acetates, particularly the salts of calcium, baryum, magnesium, or lead, or by exposing the vapours of acetic acid to a red heat on their passage through a tube. It is further one of the products of the destructive distillation of sugar, tartaric acid, cellulose, and other bodies, and occurs therefore in the common pyroligneous, or pyroacetic spirit.

Mode of Obtaining Acetone from Diabetic Urine.

The urine is acidified with tartaric acid, and distilled, until at least half the bulk has been condensed. The distillate is rectified three times, and the product distilled three times over dry sodic sulphate; the last distillate is now treated with dry potassic carbonate, and again distilled. The product thus obtained is yet contaminated with small quantities of a neutral volatile matter, smelling of rotten horse dung: from this it is separated by repeated distillation from the water-bath. It still contains

alcohol, which is fixed by letting the mixture stand with fused calcic chloride, decanting the liquid, and distilling from the water-bath. The distillate is pure acetone. The chloride of calcium compound, on decomposition with water, and distillation, yields an alcoholic fluid, which may be concentrated and treated so as to obtain pure alcohol directly, or transformed into ethylic iodide. The boiling point of the latter proves the liquid to have contained almost pure ethylic alcohol, with traces only of butylic and propylic alcohol, but probably not a vestige of amyllic.

Physical and Chemical Properties.

Acetone is a colourless, thin liquid of 0.874 sp. gr. at 0°, and boils at 56°. It is soluble in water, alcohol, and ether, and may be mixed with them in any proportion. Like alcohol, it dissolves many substances which are insoluble in water, such as resins or pigments. In contact with hydrated caustic alkali and oxygen it becomes brown, and is transformed into a resinous substance. The vapours of acetone passing over heated soda lime give off hydrogen, and are transformed into acetic and formic acid, which remain combined with the soda. The molecular formula of acetone is C_3H_6O .

Diagnosis and Significance of Acetone in the Urine of Diabetic Patients.

It has often been observed that the breath, urine, and sweat of diabetic persons has a peculiar odour which attracts attention, and is compared to various smelling substances; such observations have been recorded by Hodges ("London Med. Gaz." 1843), Hodgkin ("Assoc. Med. Journ." 1854, Nr. 93), Rother ("Preuss. Ver. Zeit." 1844, Nr. 9), Brand ("Deutsche Klinik," 1850, Nr. 6), and others. It is not necessary to state the odours to which the smell of diabetic matters (including parts of the dead body) has been compared, but it must be borne in mind that the smell has repeatedly been found to be so characteristic as to lead the physician to the diagnosis of diabetes. Observations should be made on the breath of diabetic patients for the purpose of identifying the odoriferous ingredient with the acetone and alcohol which appear in the urine.

Gerhardt had observed that diabetic urine which yielded acetone gave a reddish-brown coloration with ferric chloride. As the ethylene-dimethyle carbonic acid of Geuther (also termed ethyl-diacetic acid), $C_6H_{10}O_3$, also gives this reaction with ferric chloride, and is easily decomposed, forming acetone, alcohol, and carbonic acid, Gerhardt formed the hypothesis that diabetic urine contained this acid, and that the acetone found by its distillation was formed by its decomposition.

Rupstein tested this hypothesis upon the urine of a diabetic female, aged forty. The urine gave the red-brown colour with ferric chloride, which disappeared on heating. The fresh urine had no peculiar odour, evolved the odour of acetone after half an hour's boiling, and then did no longer give the colour with ferric chloride. Left to stand for from 8 to 14 days, the urine had lost the power of reacting with ferric chloride. Geuther's acid added to normal urine caused it to show the same phenomena as the diabetic urine. Rupstein now treated large quantities of diabetic urine, acidified by acetic acid, with ether, and found in the ether solution an acid, which became reddish-brown with ethereal solution of ferric chloride. Without previous addition of acetic acid the ether did not extract the acid in question; for which reason Rupstein assumes it to be present in the urine as sodium salt, $C_6H_9NaO_3$.

However, in this argument the substances which are normally present in healthy urine, and give a brownish-red colour to ferric chloride, are not sufficiently excluded, or accounted for; and a deepening of colour of ferric chloride is obtained with so many substances that it cannot be diagnostic of any one of them. Moreover, it is not proved that ethyl-diacetic acid, which is the ethylic ether of aceto-acetic acid, does decompose in acid solutions, and it should, according to theory, to which experience corresponds, decompose only in alkaline solution. Moreover, if the acetone from diabetic urine had this origin, it should always be accompanied by its equivalent of alcohol, or in round numbers with every 5 parts of acetone there should be obtained 4 parts of alcohol. This is, however, not the fact. Markownikoff obtained from 73 litres of urine from a diabetic boy, aged sixteen, who was melancholic, and whose breath smelled similar to the breath of persons who have inhaled chloroform, 33 grm. of anhydrous acetone mixed with alcohol. From this mixture only 3 grm. alcohol were obtained, the 30 grm. were acetone. From 82 litres of the urine of a diabetic girl he obtained only 5 grm. acetone, and with this so little alcohol that it was scarcely sufficient to determine the boiling point of its iodide. He therefore supposes that both the acetone and the alcohol appear in these cases as the products of a particular kind of fermentation of the grape sugar, and that this fermentation is caused by a particular kind of ferment produced in the diabetic body. The quantity of acetone formed is dependent upon the quantity of such ferment, which the diabetic economy may produce. This hypothesis is applicable to the case of Petters, in which acetone was first discovered.

A Jewess, thirty years old, shopwoman, was admitted into the Prague Hospital. She had undergone much privation during eighteen years. She had been treated as an out-patient for con-

stipation. Five weeks before admission she was suddenly attacked by violent pain in her stomach, and repeated vomiting. The bowels had been confined during six days. She was relieved by a purgative, and returned a week afterwards, complaining of continued great thirst, and of the necessity to pass urine more frequently and in larger quantities. The diagnosis of diabetes was established by the discovery of sugar in her urine. The symptoms continued to increase in intensity, the pain in the stomach and vomiting returned, and she at last consented to be received into the hospital.

On her arrival she vomited. Her tongue was found a little moist; the saliva had an acid reaction. The breath had a strong spirituous odour. The examination of the organs of respiration and circulation revealed no lesion. The urine was straw yellow, of a strongly acid reaction, and 1.0315 sp. gr. contained 4 per cent. of sugar, much urea, and scarcely a trace of uric acid. Besides a strong peculiar odour, it offered no peculiarities. The patient herself complained of weakness, thirst, and pain in her stomach.

On the morning after her admission she was in a sort of narcotised condition, and gave off a spirituous odour similar to that of chloroform, which was so intense, that after a little time it became perceptible in the whole ward, and was noticed by all other patients. One of the clinical assistants was misled to the opinion that chloroform had been administered to the patient during the night. The patient was almost unconscious, and lay there, the eyes half open, and all muscles relaxed. Her skin was cool, and showed 33.0° in the axilla; the face was slightly flushed, the eyes surrounded by a halo, the looks fixed. The patient was like a person half under the influence of chloroform; her extremities dropped like paralysed on being raised, and a few words could be elicited when her consciousness had been made to return for a moment by questioning with a loud voice. She had a small pulse of 92 beats per minute. The abdomen was distended with gas. As she had passed no water since the night, the catheter was applied, and a pound of urine was withdrawn, which was pale yellow, contained sugar (specific gravity 1.027), and much of the odoriferous principle. Including this quantity, the patient had only passed ninety-three fluid ounces of urine during the last twenty-four hours; the secretion of urine then ceased entirely. The swelling of the abdomen increased, she complained of much pain in the stomach in moments of returning consciousness, and died next morning, thirty hours after the beginning of this extraordinary condition.

The post-mortem examination revealed no particular lesion in any organ except the intestinal canal, which was very much distended with gas, the inner surface covered with a thick, greyish-

white mucous layer, and the inner membranes very much congested. The contents of the stomach resembled fermenting grain, and consisted of a brownish, flaky mixture, which evolved a spirituous pricking odour, and also the peculiar odour of the other secretions. It had an acid reaction, and gave the tests for grape sugar. The microscope revealed some fibres of flesh, some starch corpuscles in a disintegrating condition, and numerous yeast cells.

The urine on distillation yielded an alkaline, clear fluid, which had the odour of ammonia, carbolic acid, and an empyreumatic spirituous substance; and after neutralisation with dilute sulphuric acid and repeated rectification, allowed the characteristic odour to appear more freely. The distillate was again rectified over chloride of sodium, and afterwards once more for itself in the water-bath, when a colourless, clear fluid, strongly refracting light, of neutral reaction and biting taste, was obtained, which was easily inflammable, and burned with a bright, strongly lighting flame. Its odour was very much like that of aldehyde; it had a neutral reaction. The fluid became brown when mixed with sulphuric acid. As caustic potash produced a brown resinous body in the fluid, and solutions of oxyde of silver caused no reduction in it, it was surmised to be acetone, but it is evident that the possibility of its having contained some alcohol is not excluded.

The blood had a strong odour of acetone. But its quantity was not sufficient to isolate that substance. It contained sugar, and was faintly alkaline. The watery extract of the lungs, subjected to distillation, yielded a neutral distillate, smelling of newly-baked bread, which, after repeated rectification, with addition of sulphuric acid, and afterwards of chloride of sodium, lastly after distillation from the water-bath gave drops which strongly smelled of acetone, yielded the above reactions, and were combustible.

The presence of acetone in the urine and blood was therefore established, and it is most probable that to the anæsthetic effect of this substance, diffused through the whole system as it was, the comatose condition and fatal end of this case were due.

The contents of the stomach did not yield acetone, but alcohol seemed to be present. The mucus of the glandular surface of the stomach, after the latter had been washed with distilled water, was found to possess the property of transforming starch into sugar and gum, and sugar into alcohol and carbonic acid. The contents of the stomach possessed the same power, which is not possessed by normal gastric juice. The influence of saliva was carefully excluded in the experiment with the mucus from the glandular membrane of the stomach.

CHAPTER LVII.

ALLANTOINE, $C_4H_6N_4O_3$.

HISTORY AND LITERATURE.

ALLANTOINE was discovered in 1800 by Vauquelin and Buniva ("Ann. Chim." 33, 269) in the allantoic fluid of the cow, which was mixed with amniotic. Lassaigne ("Ann. Chim." 42, 406) showed that the substance was peculiar to the allantoic fluid. Liebig and Wöhler ("Ann. Chem." 26, 244) discovered allantoin as a product of the oxydation of uric acid, and Wöhler ("Ann. Chem." 70, 229) found it to be a natural ingredient of the urine of sucking calves. Städeler once obtained allantoin from the urine of a dog, into whose veins oil had been injected, and who was suffering from dyspnoea in consequence.

Mode of Obtaining Allantoin.

The allantoic fluid of the cow (which is mostly mixed with amniotic liquor) is evaporated to one quarter of its original bulk, and cooled down to make allantoin crystallise. Allantoin is also precipitated from the fluid when it is allowed to stand for some length of time, and may then be separated, dissolved in hot water, and, after filtration, recrystallised.

The urine of calves is obtained by tying the bladder before the animals are killed by the butcher. This proceeding can only be adopted in countries where the calves are killed very early, as in Germany and Switzerland. In this country, therefore, other proceedings must be had recourse to for obtaining the urine. Among those which are practicable, the catheterism of female animals appears to be most suitable. The urine thus obtained is evaporated on the water-bath to a syrupy consistence, and is put in a cold place for several days, then diluted with water. The gelatinous precipitate of urate of magnesium is then removed by washing, when there remain only crystals of phosphate of magnesium and allantoin. They are now washed with a little cold water, boiled with water and a little good animal charcoal, and filtered, when most of the phosphate of magnesium remains on the filter. The addition of a few drops of hydrochloric acid to the filtrate keeps in solution the phosphate of

magnesium, and, on cooling, colourless allantoinine crystallises from the solution.

The urine of dogs suffering from dyspnoea by injection of oil into the veins, immediately after passing, is precipitated with basic acetate of lead, and the excess of lead removed from the filtrate by sulphuric acid and hydrothion. The colourless fluid is evaporated on the water-bath. The residue is extracted with boiling spirit of wine of 82 per cent., and the yellowish solution put aside in a well-closed bottle. After the lapse of several days a large quantity of small white groups of crystals appear deposited upon the sides of the bottle, which are almost insoluble in cold water, but dissolve in boiling water, and on cooling are deposited again in larger glistening crystals.

Powdered uric acid is suspended in little water, and heated to near the boiling point. Peroxyde of lead in a finely powdered state is now added to the fluid, which is continued to be kept hot, until the last portions of the peroxyde are no longer transformed into a white mass. The mixture is now filtered hot, and the filtrate, on cooling, and on further evaporation and cooling, yields allantoinine in crystals; the mother-liquor contains urea, from the last traces of which the crystals of allantoinine may be separated by recrystallisation.

Physical and Chemical Properties.

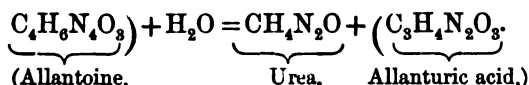
Allantoinine crystallises in glass-like needles, which have the composition $C_4H_6N_4O_3$; when obtained from uric acid it represents rhombohedric crystals, combined with the hexagonal prism or column. It is tasteless, colourless, and has no reaction on test-paper. Exposed to the air it undergoes no change; it contains no water of crystallisation.

Allantoinine is soluble in 160 parts of cold water, in 30 of boiling water; it is soluble in hot alcohol, and crystallises from both these hot solutions on cooling. It is soluble in cold solution of caustic potash, and is precipitated from this solution by the addition of acids. If, however, allowed to remain in this solution for any length of time, it is metamorphosed. It is soluble in solutions of the carbonates of the alkalies. When boiled with hydrate of potassium or baryum it is resolved into ammonia and oxalic acid. The same decomposition takes place under the influence of yeast, at a temperature of 30° . Urea, oxalate and carbonate of ammonium, and a new acid, not investigated, are the products of the decomposition.

Subjected to dry distillation, it yields carbonate and hydrocyanate of ammonium, empyreumatic oil, and a spongy charcoal. Heated with oil of vitriol it is decomposed into sulphate of ammonium and a mixture of carbonic acid and oxyde.

When gently warmed with nitric acid of a specific gravity of

1.2 to 1.4, during which process no gas is evolved, the solution on cooling yields nitrate of urea in crystals. The solution, on being evaporated to dryness, leaves nitrate of urea and allanturic acid—



The same decomposition of allantoine can be brought about by boiling it with hydrochloric acid, and by heating it enclosed with water in a strong tube to a temperature of from 110° to 140°. Here urea is further decomposed into ammonia and carbonic acid.

On adding to a boiling saturated solution of allantoine in water nitrate of silver, and then ammonia, so long as a precipitate is being formed, a combination of allantoine with (oxyde of ?) silver, $\text{C}_4\text{H}_5\text{AgN}_4\text{O}_3$, is obtained, which is a white glistening powder, and under the microscope appears in spherical balls. It is decomposed by all dilute acids, allantoine being set free.

A solution of allantoine is not precipitated by corrosive sublimate. It is, however, precipitated by a solution of nitrate of oxyde of mercury, and, like urea, combines with mercury in various proportions, analogous to the compounds of urea.

It enters into combination with the oxydes of copper, cadmium, lead, and zinc, and the combinations crystallise.

Physiological and Pathological Indications.

In consequence of allantoine having been found in the urine of dogs suffering from dyspncea following the injection of oil into their veins, several inquirers examined the urine of persons suffering from dyspncea, emphysema, and pneumonia, as also the urine of a woman who, to relieve the dangerous dyspncea caused by an aneurism of the arch of the aorta, had tracheotomy performed upon her. In neither of these cases were the observers able to find allantoine in the urine. It is therefore yet questionable how the appearance of allantoine in the urine of the dog has to be explained. It is also a question whether allantoine ever appears in the urine of man. But as there is a probability, and as it has been stated that it occurs in human amniotic fluid and in the urine of infants during the first eight days after birth, I have thought it best not to omit the description of its properties, in order that there might be less chance of its being overlooked by future observers.

Köhler ("De Allantoine in Urina impedita respiratione præsentia," Diss. Halens. 1857) repeated the experiment which Städeler made upon a dog upon some rabbits, and believed that he had found allantoine. Meissner and Jolly gave to dogs much

fat and some succinate of soda with their food, and believed that they had found allantoin in the urine as a consequence of this diet. Schottin found it in human urine after the taking into the stomach of large quantities of tannin. If the former observers can hardly be said to have proved their cases, Schottin's assertion must be decidedly objected to as untrustworthy on the ground stated under the chapter on Kreatinine.

E. Salkowsky ("Ber. Deutsch. Chem." G. 9 (1876), 719) gave uric acid to dogs, and found that the nitrogen in the urine could thereby be increased to the amount of $1\frac{1}{2}$ gm. per day. This was mainly due to the appearance of allantoin in the urine. It could be obtained crystallised by evaporating the urine to $\frac{1}{4}$ or $\frac{1}{5}$, and letting it stand. In the urine of one dog allantoin appeared as a sediment on cooling. From the urine of a dog, which had taken on each of two days 4 gm. of uric acid, 1.42 gm. of allantoin were obtained. Oxalic acid appeared only in very small quantity, uric acid in traces. Whether any urea is formed from the ingested uric acid is undecided.

CHAPTER LVIII.

OXALURIC ACID, $C_3H_4N_2O_4$

HISTORY AND LITERATURE.

THIS acid was discovered by Liebig and Wöhler ("Ann. Chem." 26 (1838), 287 as a product of decomposition of uric acid. Schunck ("Proceed. Royal Soc." 16, (1867) 140) obtained oxaluric acid from normal urine.

Mode of Obtaining from Uric Acid and its Derivates.

A solution of uric acid in warm, very dilute nitric acid is mixed with ammonia and evaporated immediately. After cooling it yields crystals of oxalurate of ammonia, which must be decolorised by animal charcoal. Or parabanic acid is dissolved in aqueous ammonia and heated to the boiling point; on evaporation and cooling ammonic oxalurate crystallises. Carbonate of lime dissolved in watery parabanic acid yields a solution of calcic oxalurate. To obtain free oxaluric acid from the ammonia or the calcium salt, it is dissolved in a small quantity of warm water, mixed with sulphuric, hydrochloric, or nitric acid, the liquid cooled as quickly as possible, and the pulverulent deposit of oxaluric acid washed and dried.

Mode of Obtaining from Human Urine.

The urine is filtered through animal charcoal. The oxalurate remains in the charcoal, and can be extracted by boiling it with alcohol, after it has previously been washed with water until the filtrates were free from chlorine and phosphoric acid. The alcoholic solution is evaporated or distilled; the last portions evolve a strong odour of urine oil. The residue is treated with water, which leaves a fatty acid, and the solution on long standing deposits impure oxalurate, which is purified by recrystallisation, animal charcoal, or dialysis. 150 litres of urine yield only a small quantity of the salt; and it is worthy of being inquired into whether the oxaluric acid in this method is not produced by the oxydising influence of the charcoal upon the dissolved uric acid of the urine.

Physical and Chemical Characters.

The acid is a white crystalline powder, which has an acid taste and reddens litmus. It is very little soluble in water, but dissolves easily in combination with alkalis. When a watery solution of oxalurate of ammonia is mixed with caustic ammonia and calcic chloride, no reaction is at first produced; but when the mixture is gently heated a white precipitate of calcic oxalate is produced. Oxaluric acid is decomposed in a similar manner by a moment's boiling with hydrochloric acid; the solution with excess of ammonia and calcic chloride gives a precipitate of calcic oxalate.

The ammonia salt forms silky needles, which are stable at 120° , little soluble in cold water, but more readily soluble than the free acid, and easily soluble in hot water.

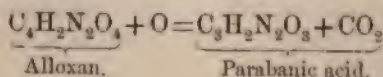
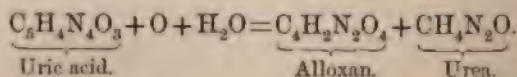
The calcium salt, which is obtained by mixing concentrated solutions of ammoniac oxalurate and calcic chloride, is neutral, and forms shining crystals, which are but little soluble in water. The basic salt, on the other hand, is obtained by adding excess of lime water to the acid, or by mixing the neutral salt, or the clear mixture of ammoniac oxalurate and dilute calcic chloride with ammonia. It forms a thick gelatinous precipitate, which dissolves sparingly in water, readily in dilute acids, even in acetic acid.

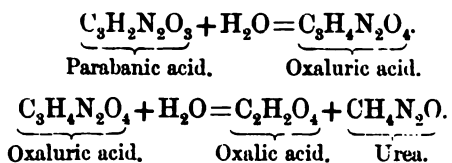
The silver salt is produced in a crystallised state by mixing alkaline oxalurate with silver nitrate; the white flakes either crystallise spontaneously on standing, or after solution in hot water and standing, in delicate silky needles. The crystals are anhydrous, and when heated decompose without any explosive action.

The Physiological and Pathological Relations

of oxaluric acid have not yet been investigated. If under pathological conditions it occurred in larger quantity, its decomposition in the bladder might perhaps produce oxalic acid, and furnish means towards the formation of oxalate of lime calculi. But as it is not yet certain whether the oxalurate obtained from urine is not produced by the oxydising action of the charcoal employed, further speculation on this subject is superfluous.

The equations according to which uric acid can be made to yield oxaluric and oxalic acid are the following:—





Whether such a process as this ever takes place in the animal body is very doubtful. Uric acid is a terminal product of a firm chemical constitution ; when reintroduced into the body, it is oxydised no further than to the stage of allantoin, as has been shown under the chapter relating to that substance.

CHAPTER LIX.

OXALIC ACID, $C_2H_2O_4$.

HISTORY AND OCCURRENCE.

THE *sal acetosellæ* had been known and used for a long time, when Scheele ("Opusc." 2, 187) in 1774 described a proceeding of separating oxalic acid from it by lead acetate, and also discovered (*ibid.* 3, 364) the identity of this sorrel acid with the acid found by Bergmann to be the principal product of the oxydation of sugar by means of nitric acid.

Oxalic acid is one of the most frequent products of the oxydation of organic matter by artificial processes. Its compounds are very frequent in plants, where the acid represents most probably the first stage of the reduction of carbonic acid. Thus, binoxalate of potassium was formerly manufactured from certain species of *oxalis*, in which, as in certain species of polygonaceous plants, such as *rumex* and *rheum*, it is found in considerable quantities. The parallel sodium salt is found in certain plants familiar at the seashore, or in the neighbourhood of salt-works, *salicornia* and *salsola*. Oxalate of lime enters largely into the construction of many species of lichen, growing on rocks of limestone; it frequently amounts to one-half of their weight. Most higher plants contain smaller or larger quantities of the calcareous oxalate. In the animal organism oxalic acid is rarely met with, except in the insoluble form of the oxalate of lime when taken in vegetable food. Oxalic acid occurs free in urine, when large quantities of oxalic acid or oxalates are taken in repeated doses. After the ingestion of these substances, the urine also contains calcic oxalate in form of a precipitate.

Oxalic acid, mostly in form of the calcic oxalate, occurs in the urine in the course of certain diseases. It is at present unknown whether the oxalic acid in these cases is a product of the organism itself, and, like the acid after ingestion into the stomach, is carried by the blood to the kidneys to be there secreted, or whether the acid is the product of a certain and peculiar decomposition of urine in the urinary passages.

Normal human urine, after some standing, mostly deposits

microscopical traces of oxalate of lime, not approachable by quantitative analysis. The normal urine of herbivorous animals mostly contains a more appreciable quantity of the oxalate.

Mode of Producing Oxalic Acid.

One part of sugar is heated with six parts of nitric acid of 1.3 sp. gr., until red vapours are no longer evolved. The fluid on evaporation on the water-bath yields oxalic acid in crystals, amounting to one-third of the weight of the sugar employed.

Physical and Chemical Properties.

From its watery solution oxalic acid crystallises in monoclinometric prisms, containing two molecules of water of crystallisation, and hence having the composition $C_2H_2O_4 + 2H_2O$. In dry air it loses the whole of the water of crystallisation, and transforms into a white powder. It is soluble in nine parts of cold water, much more soluble in boiling water or alcohol.

On being heated it fuses, and at a temperature of 155° to 160° it is decomposed, yielding carbonic and formic acid, the latter being further decomposed into carbonic oxide and water.

When oxalic acid is dissolved in glycerine and heated it is decomposed to carbonic and formic acid only, $C_2H_2O_4 = CO_2 + CH_2O_2$. The formic acid can be obtained pure by distillation. When heated with concentrated sulphuric acid, oxalic acid is decomposed so as to yield equal volumes of carbonic acid and carbonic oxide, the water formed at the same time being retained by the sulphuric acid. Oxydising agents transform oxalic into carbonic acid; this is effected slowly by nitric acid, quicker by chlorine water, peroxyde of lead or manganese, rapidly by a solution of potassic permanganate.

Oxalic acid is a powerful acid, and displaces many weaker acids from their combinations. It is dibasic, so as to form neutral salts with two dynamicities of metal, $C_2M''O_4$, and acid salts with one dynamicity, $C_2Hm'O_4$. It also forms so-called quadroxalates of the formula $C_2Hm'O_4 + C_2H_2O_4$. The salts of the alkali metals are easily soluble in water and insoluble in alcohol. The salts of the alkaline earth metals are quite insoluble, so that calcium and oxalic acid constitute the best precipitants for each other in alkaline solutions. The oxalates of metals are mostly insoluble or little soluble in water.

Calcic oxalate, $C_2CaO_4 + H_2O$, and another form with $3H_2O$, is obtained by mixing solutions of calcic chloride and an alkaline oxalate in the form of a white crystalline powder, which consists of minute crossed prisms of the quadratic system. When

obtained from concentrated and hot solutions, it only contains one H_2O , but when obtained from dilute cold solutions it is a mixture of the mono- and trihydrate. Exposed to dry air at 100° the mixed salt loses half its water of crystallisation; the other half is expelled at 200° . The monohydrate loses half its water at 180° . It is necessary to keep the salt covered during the drying process, as at 150° it becomes very electrical, so as to be thrown out of the dish at the slightest touch. It is insoluble in water and acetic acid, soluble in hydrochloric and nitric acid. From solutions in the latter acids it may sometimes be obtained in crystals by slow evaporation. From the solution in hot concentrated hydrochloric acid a double salt of calcic chloride and oxalate is sometimes obtained in crystals. Free oxalic acid in crystals is also obtained from the solution. The crystals of double salt, when brought in contact with water, are decomposed into calcic chloride, which dissolves, and calcic oxalate which remains as an insoluble powder. If the free oxalic acid has not been separated from the double salt by alcohol, or the double salt has not been isolated mechanically, no calcic chloride is obtained after resolution of the crystals, as it is immediately decomposed by the oxalic acid.

Phenomena of Crystallisation and Polarisation of Calcic Oxalate.

All varieties of crystals which I have as yet met with may be brought under one of the following forms:—

Quadratic octahedron.—Primary axis always shorter than secondary axes.

Crossed octahedra, or tropias, imitating the appearance of crossed octahedra.

Quadratic octahedron and prism combined.—The same combination, to which a second prism is added.

Crossed prisms.

Triple twins, with tropia.

Modifications of crossed octahedra by a secondary twin tropia, affecting the points of the octahedra.

Contortions and Anomalies.—Dumb-bells, being prisms with apposition of irregular matter to both octahedral ends, the prismatic sides frequently to be distinguished.

Pure calcic oxalate can readily be ascertained to possess the power of polarising light. But the ordinary oxalate, the octahedra, have a very faint polarising power, which can only be brought out fully by reflecting a ray of the sun through the crystal lying between the two Nicol prisms, and excluding from the eye every other light but that coming from the crystal in the microscope.

The explanation of the fact that the ordinary octahedra polarise very faintly seems to be that, as they are very flat, their principal

axis is mostly standing almost perpendicular. Now as a crystal polarises the less, the more parallel with its principal axis are the rays of polarised light passing through it, it is probable that the octahedra polarise only little, because the polarised light passing through them is almost parallel to their principal axis.

There is no optical reason for assuming octahedra and dumb-bells to be made up of different materials. And as there is no chemical evidence for the supposition that the dumb-bells consist of oxalurate of lime, they must for the present continue to be ranged under the oxalate, with which, indeed, G. Bird proved them to be identical by the five experiments intended to show that they were oxalurate of lime.

Mode of Determining the Quantity of Oxalic Acid in Urine.

Oxalic acid, which may be present in the urine in a free state, is transformed into a precipitate, by first adding to the urine, previously neutralised by ammonia, some acetic acid, and then chloride of calcium. The precipitate, after several hours' or days' standing, is separated by decantation and filtration. The oxalate thus obtained may be transformed into the sulphate or it may be analysed volumetrically by potassic permanganate.

Physiological and Pathological Significance of Oxalic Acid in Urine.

The presence of oxalic acid or any of its compounds in urine may indicate that oxalic acid or any of its compounds has been introduced into the stomach, as an ingredient of food, as a medicine, or as a poison. Wöhler was the first to prove that oxalic acid when taken into the stomach might reappear in the urine. Buchheim repeated his experiments and obtained their confirmation in every instance.

The presence in the urine of any considerable quantity of oxalic acid, in any form, for a longer period of time, during which the ingestion of oxalic acid, in any form, into the stomach was excluded, indicates the existence of a disease termed "oxalic acid diathesis," or "oxaluria," which is distinguished by a great tendency to the production of calcic oxalate concretions in the urinary passages. It is not ascertained whether in these cases the oxalic acid is formed in the circulation, or only in the urinary passages, by a peculiar kind of fermentation of some normal or abnormal ingredient of the urine.

Calcic oxalate is frequently found in not very small quantities in the urine of patients recovering from severe acute diseases. Thus the first urine which is voided by cholera patients after long-continued suppression contains calcic oxalate. The quan

tity is ascertained by collecting the deposit of oxalate and precipitate produced by calcic chloride, on a filter, and after washing, dissolving it in hydrochloric acid. To the solution gold perchloride is added, and the mixture is boiled until no further reduction takes place. From the weight of the brownish-violet, diroic precipitate of metallic gold, the quantity of oxalic acid present in the solution is calculated. 31 parts of metallic gold indicate 30 parts of oxalic acid.

Examples.—The first urine of a patient recovering from cholera collapse measured 457 c.c., and contained 278 milligram. or 0.6 per mille of oxalic acid. A similar quantity from a second case gave 58 milligram. or 0.125 per mille of oxalic acid. Thirteen ounces of urine contained three-quarters of a grain of oxalic acid. A third case excreted a similar quantity, containing 117 milligram, or 0.25 per mille of oxalic acid. Thirteen ounces contained a grain and a half of the acid.

The presence in urine of such small microscopical traces of calcic oxalate, that its amount cannot be estimated by quantitative analysis, is of no practical or pathological importance. The question after its origin is one of the greatest difficulty.

The presence of calcic oxalate in the urine may indicate disease of the kidneys, with which it is not rarely associated. The relations between the oxalate and the kidney disease are however uncertain. Experiment shows that large quantities of oxalic acid passing through the kidneys may so irritate them as to cause albumen to transude into the urine. It is therefore not unreasonable to think that in some cases of disease or poisoning a similar relation may exist.

In the following case considerable quantities of calcic oxalate were present in albuminous urine of a patient, who succumbed to disease of the kidneys:—A married woman, æt. 30, dated her illness from her last childbed, about 18 months before the time at which she came under treatment. The delivery had been difficult, and had resulted in prolapsus uteri. The urine then became habitually turbid, she lost flesh, became anasarctous, and yet when I saw her, she was again in the sixth month of a new pregnancy. She had an abscess at the outer side of the middle of the left thigh. The urine was turbid on expulsion, and became still more so on standing. Sometimes it contained a little blood. When this urine was allowed to stand in the water-bath at the temperature of the body, it deposited a considerable amount of almost pure oxalate in octahedra, mixed with some casts of the urinary tubules. The patient soon after died of uræmic coma. In no part or liquid of her body, the urine excepted, could any oxalic acid be discovered by microscopical or chemical quiry.

*Experiments on the Reappearance of Oxalic Acid in the Urine
after Ingestion into the Stomach.*

Wöhler made a middle-sized dog eat two drachms of powdered oxalic acid mixed with meat and bread. After the dog had been killed eight hours later, there were found three ounces of urine in the bladder, which did not appear to be more acid than usual. On the urine becoming cool, there was deposited a considerable quantity of white powder, consisting of small crystals very much like triple phosphate. On mixing the decanted clear urine with a solution of nitrate of lime, another precipitate of a similar description, and in the same quantity as the first spontaneous one, was obtained. Both precipitates on examination were proved to be pure oxalate of lime. They transformed into carbonate of lime mixed with some charcoal on exposure to red heat, did not evolve any ammonia by heat or fusion with potash, were quietly soluble in nitric acid, and again precipitated in a crystalline state by ammonia. When heated with a solution of carbonate of ammonia, carbonate of lime was formed, and the filtrate on evaporation yielded a crystalline salt, having all the properties of oxalate of ammonia. Besides these ingredients, the urine contained a considerable quantity of albumen. The precipitate obtained by nitrate of lime most probably contained some phosphate of lime.

Piotrowsky, under Buchheim's directions, has repeated these experiments upon himself. In order to ascertain the degree of accuracy with which oxalic acid in urine could be determined quantitatively, the urine of twenty-four hours, amounting to 987·8 grm. was mixed with a solution of 1·0 grm. of crystallised oxalic acid, which had before been neutralised by ammonia. The mixture was evaporated to one-sixth of its original bulk strongly acidulated with acetic acid to keep phosphate in solution, and then had some chloride of calcium mixed with it. The precipitate, after standing for several days, was collected on a filter, pressed between bibulous paper, and dissolved in hydrochloric acid; from the solution uric acid was removed by filtration; the filtrate was neutralised with ammonia, and again acidulated with acetic acid. The oxalate of lime thus obtained after filtration and drying, at a temperature of 120° amounted to 1·087 grm., corresponding to 0·931 grm. of crystallised oxalic acid. The same proceeding was adopted in the following experiments.—

(a.) *Free Oxalic Acid.*—1. Five grm. of crystallised oxalic acid, in doses of 1 grm. each, were taken in the course of five hours, and the urine was collected during twenty-four hours from the beginning of the experiment. It was very turbid after a few hours. When filtered it did yet contain some salts of lime, showing that all

the lime was not combined with oxalic acid. The total quantity from the twenty-four hours was 1588.5 gm., and yielded 0.418 gm. of anhydrous oxalate of lime, corresponding to 0.4115 gm. of crystallised oxalic acid, being 8.23 per cent. of the quantity taken.

2. Seven gm. of oxalic acid were taken in the course of six hours. The thick, neutral urine, whose quantity was 1443.4 gm., contained the oxalate of lime almost exclusively in the shape of dumb-bells. After it had been evaporated, acidified, and left standing for several days, the filtrate gave no evidence of the presence of lime, but the addition of chloride of calcium produced a fresh precipitate. The first precipitate, free from water, amounted to 0.735 gm., the second to 0.241 gm. together corresponding to 0.961 gm. of crystallised oxalic acid, being 13.72 per cent. of the quantity taken.

3. Seven gm. of oxalic acid were taken, as in Exp. 2. The urine amounted to 1380.2 gm.; the first precipitate to 0.766 gm., the second to 0.157 gm., together corresponding to 0.909 gm. crystallised oxalic acid, or 12.98 per cent. of the quantity taken.

4. Eight gm. of oxalic acid were taken in the course of several hours. The quantity of the acid turbid urine was 1513 gm.; that of the first precipitate, 0.878 gm.; that of the second, 0.302 gm., corresponding to 1.162 gm. of oxalic acid, or 14.52 per cent. of the quantity ingested.

(b.) *Oxalate of Soda*.—5. Seven gm. of oxalic acid were neutralised with carbonate of soda, and the solution was evaporated to dryness. The salt thus obtained was taken in six doses in the course of several hours. The quantity of acid turbid urine voided in the subsequent twenty-four hours was 1678.6 gm. The spontaneous precipitate amounted to 0.759; the second, artificially produced, to 0.296 gm., corresponding to 1.039 gm. of crystallised oxalic acid, equal to 14.84 per cent. of the quantity taken.

(c.) *Acid Oxalate or Binoxalate of Soda*.—6. Four gm. of oxalic acid were neutralised with carbonate of soda. To the solution four gm. of oxalic acid were added, and the fluid evaporated to dryness. The residue was taken in several doses. It created considerable thirst, and the quantity of urine rose in proportion to the amount of water drunk, to 2976.3 gm. The first precipitate weighed 0.883 gm., the second 0.324 gm., together corresponding to 1.188 gm. of crystallised oxalic acid, being 14.85 per cent. of that taken.

(d.) *Oxalate of Lime*.—7. Seven gm. of oxalic acid were neutralised with ammonia, and precipitated with chloride of calcium. The dried precipitate was taken by an individual who had not served for any experiments with oxalic acid. The urine

amounted to 1215·4 grm., was acid, somewhat turbid, and made only a slight deposit, which, under the microscope, consisted of crystals of oxalate of lime, and amounted to 0·105 grm., corresponding to 0·1034 grm. of oxalic acid, being 1·477 per cent. of the amount ingested. The urine did yet contain some lime in solution. In the normal urine of the same person, which was collected a few days afterwards, and amounted to 1264·4 grm., no appreciable quantity of oxalate of lime could be detected.

8. A second experiment was made with another individual, whose urine under the microscope exhibited a few scattered crystals of oxalate of lime, which could, however, not be determined by weight; seven grm. of oxalic acid, in the form of oxalate of lime, were taken. The urine was more turbid than in the former experiment, and yielded 0·118 grm. of oxalate of lime, corresponding to 0·1162 grm. of crystallised oxalic acid, or 1·659 per cent.

The specimens of oxalate obtained in the last two cases were each exposed to red heat, dissolved in dilute hydrochloric acid, and treated with some chloride of baryum. In both an insignificant turbidity ensued, so that they could have contained only very small quantities of gypsum.

The experiments show that large quantities of oxalic acid may be taken with impunity if taken in hourly, or otherwise divided, doses. They do not militate against the fact that oxalic acid, taken in doses of half a drachm to one or two drachms *at a time*, is a deadly poison. They also prove that a part of the oxalic acid in any form, taken in larger and repeated doses, makes its reappearance in the urine, partly as oxalate of lime, partly as a soluble oxalate; but the larger proportion of the oxalic acid taken disappears in the system, without appearing in the urine as carbonate, in cases where the acid or neutral salt has been taken. The quantity of oxalic acid passing into the urine is not different, if oxalic acid be taken as such, or in combination with alkalies. But if taken in combination with lime, only a small percentage of the oxalic acid reappears in the urine, because the greater part of the oxalate of lime passes unchanged through the intestines, and is discharged with the feces, as was proved by Magawley and Buchheim in two experiments. In two experiments with oxalate of magnesia, this salt seemed to be decomposed in the intestinal canal in larger quantity than the lime salt. The quantity of lime in the urine after ingestion into the stomach or oxalic acid, or its salts, is neither increased nor diminished.

The following table perspicuously exhibits the results of the above observations:—

No. of experiment	Form in which Oxalic Acid was taken.	Quantity of Oxalic acid taken.	Percentage in the Urine of Oxalic acid taken.	Spontaneous precipitate of Oxalate of Lime, anhydrous.	Lime from spontaneous Oxalate.	Oxalate of Lime from soluble Oxalate.
I.	$C_2H_2O_4 + 2H_2O$	5.0	8.23	0.418	—	—
II.		7.0	13.72	0.735	0.322	0.241
III.		7.0	12.96	0.706	0.335	0.197
IV.		8.0	14.52	0.978	0.384	0.202
V.	$C_2Na_2O_4$	7.0	14.84	0.759	0.222	0.226
VI.	$C_2Na_2O_4 + H_2O$	8.0	14.85	0.983	0.386	0.254
VII.	$C_2CaO_4 + 2H_2O$	7.0	1.477	0.105	—	—
VIII.		7.0	1.659	0.118	—	—

Concretions of Calcic Oxalate; Sand and Gravel.—Small concretions of calcic oxalate of the size of uric acid sand are rarely, if ever, met with. But there is a variety of oxalate concretions, of small size, pale colour, and smooth surface, and usually containing some urates. They are most frequently found in the calyces of the kidneys, and being many in number they exhibit the effects of prolonged attrition. These concretions, termed *hemiposed calculi*, or gravel, are not seldom passed by elderly persons after severe nephritic attacks characterising the passage through the ureters of concretions.

Renal concretions of oxalate of calcium are frequently of a very large size, particularly when uric acid has supervened. The pain and derangement caused by oxalate concretions in the kidneys usually assume different characters from the pain and derangement attending lithic acid concretions. The pain is generally of a more acute character; and though principally referred to a particular spot over the region of the kidney, is often discursive, and shoots in the direction of the ureter, epigastrium, or shoulder.

Renal hæmorrhage, referable to concretions, becomes very much more frequent after epidemics of cholera in London. It remains to be ascertained whether the occurrence of calcic oxalate in the urine of cholera patients has any share in the production of these concretions.

Calculi of Calcic Oxalate.—The purest concretions of calcic oxalate are the white crystallised variety.

Though the greater proportion of the oxalate of lime calculi have an amorphous or only crystalline texture, there are some not very rare specimens, which on their surface are covered with the most perfect crystals. I had an opportunity of closely

examining several such calculi contained in the Museum of the Royal College of Surgeons.

C. 34. Presented by Mr Luke. A reddish-brown calculus, is covered with white glistening crystals. They are octahedra, the principal axis of which is not much shorter than the two horizontal ones. The principal axis of the crystals averages in length from about one-fortieth of an inch to one-eightieth of an inch.

C. 35. Presented by Mr Luke. In this specimen the greenish octahedra are very flat, so that the principal axis is not longer than about one-third of one of the secondary axes. The sides of the longest crystals measured one-eighth of an inch. They are so arranged on the surface of the calculus as to present their lateral edges, the bodies of the crystals being buried in the calculus.

C. 1. Presented by Sir E. Home. This spherical calculus consists throughout of crystallised oxalate of lime. The crystals are smaller, and some octahedra present appearances as if their substance had been arranged in layers horizontal to the principal axis. Here and there the crystals are flattened in the direction of the principal axis, and present the appearance of square plates, sharpened at each of the four sides by two octahedral planes.

The mode in which the large crystals are deposited on these calculi leaves no doubt of their having been formed in the bladder from a solution of oxalic acid and lime. On a section, these and the crystalline calculi exhibit peculiar crystalline fibres, running from the centre in irregular curved lines towards the periphery, and mostly ending in the projections which give these calculi their peculiar uneven surface. Though layers may be distinguished, yet they are not so distinct, nor so regular, as in the uric acid concretions.

The peculiar tuberculated surface of the smaller variety of the oxalate concretions has caused the name of *mulberry calculi* to be applied to them.

The colour of those oxalate of calcium calculi which are of more frequent occurrence than the white crystallised variety is generally deep brown, sometimes approaching to very dark olive-green. This olive-green shade is also exhibited by most microscopical crystals. In some calculi the colour becomes brownish-black. These calculi are mostly very hard.

Layers of Oxalate of Calcium in Alternating and Mixed Calculi.

The most simple alternating calculus to be here considered is an oxalate stone, with a crust of phosphate, or mixed phosphates. This phosphatic crust is the produce of the decomposition of

urine caused by the presence of the calculus in the bladder. Calculi, in which a nucleus of the oxalate, however large, is surrounded by a body of uric acid, suggest a different history. Here the condition of the urine, which gave rise to the oxalate concretion, must have changed. The reverse is the case in calculi having a uric acid nucleus, and one or more layers of calcic oxalate. A nucleus of oxalate may be surrounded by a mixed body, generally consisting of oxalate, uric acid and urates, rarely of cystine and phosphates. Most mixed calculi, or mixed layers of alternating calculi, contain smaller or larger quantities of calcic oxalate.

Chemical Characters of Calcic Oxalate Concretions.

The powder of such a concretion is not affected by acetic acid; dilute mineral acids, however, dissolve it without effervescence. From the latter solution it is precipitated by an excess of ammonia. A small piece of the concretion heated before the blowpipe at first becomes black, from the admixture of a variable, but always small, quantity of organic matter, mostly urates and epithelium. It then becomes white, and ultimately leaves a bulky residue, which when moistened with water exerts an alkaline reaction on red litmus paper, and effervesces with acids. The residue is therefore calcic carbonate, with an admixture of caustic lime.

Relative Frequency of Calcic Oxalate Concretions.

The general proportion of calculi, into the nucleus of which oxalate largely enters, in all the museums, is as 1 : 4 $\frac{1}{2}$; which is equivalent to saying, that if a mulberry stone had not been formed and detained in the bladder, two persons out of about nine who suffer from calculus would not have been troubled with that affection. The general proportion of calculi consisting essentially of calcic oxalate to all other calculi is as 1 to 15. The ratio in which in alternating calculi the calcic oxalate succeeds to uric acid is as 1 to 15 $\frac{1}{2}$; on the contrary, the ratio in which uric acid succeeds to calcic oxalate is as 1 to 13 $\frac{1}{2}$. Hence the alternation of the two ingredients may be considered as nearly equal. The calcic oxalate succeeds to the ammonic urate more frequently than to uric acid. Thus the ratio in which the calcic oxalate succeeds to the ammonic urate is 1 to 9 $\frac{1}{2}$. On the contrary, the ratio in which the urate succeeds to the oxalate is only as 1 to 38; a very striking distinction. The phosphates succeed to the oxalate in the proportion of 1 to 7 $\frac{1}{2}$, and the proportion in which the oxalate succeeds to the phosphates is as 1 to 253 $\frac{1}{2}$ only.

CHAPTER LX.

LEUCINE AND TYROSINE.

OCCURRENCE.

LEUCINE and tyrosine are constant products of the treatment by concentrated or dilute sulphuric or hydrochloric acid, and by caustic alkalies of albumen, fibrine, caseine, muscle, gelatine, gluten, legumen, wool, and horn. They are also produced by the putrefaction of these substances, mostly together with some glykokoll and a series of other remarkable substances. They occur in certain pathological conditions of the organisms, such as typhus and variola, in the urine, blood, and bile. In the urine the leucine may be partly transformed into valerianate of ammonium. The liver seems to be the organ in which, during such diseased processes, leucine is formed during life, and where it is found most abundantly after death. In the liver of healthy human subjects and of animals leucine has not yet been found. In cases of acute malignant jaundice the finer branches of the hepatic veins are filled with crystalline granules, and firm, yellowish-grey strings of matter containing crystals in the shape of balls with a radiary arrangement, and bundles and sheaves of needles. The balls are leucine, and the needles tyrosine. Leucine without tyrosine occurs normally in the pancreas of animals and man, and in other smaller glands.

Mode of Obtaining Leucine and Tyrosine.—Any of the matters enumerated above will yield these substances, but horn shavings and the dry residue from the preparation of Liebig's extract of meat, which is now largely imported into Europe as a manure, are the most advantageous materials for operations on a large scale. 1 kilogram. of the finely-subdivided material is dissolved in a mixture of 1300 grm. of sulphuric acid hydrate, with about 8 litres of water contained in a leaden dish, and boiled for three hours. The mixture is then treated with excess of milk of lime, and placed into a capacious still, to be boiled for another three hours. A sulphur compound and all volatile alkalies are thus expelled and obtained in the distillate. The mixture is now filtered through a cloth, and the residue pressed strongly. The liquid is evaporated, filtered from gypsum and calcium c

acidified with acetic acid, and further condensed and allowed to stand. All tyrosine is deposited as a crystalline matter, and removed by filtration. From the filtrate calcium is removed by oxalic acid, the excess of this by lead acetate, the excess of the latter by hydrothion, and the fluid evaporated, whereupon leucine crystallises, and may be removed by filtration. From the syrup aspartic and fluorescentic acids, and fluorescentine can be obtained by various processes.

Several authors recommend the employment of much larger proportions of sulphuric acid, and prescribe boiling during nine, one even during thirty-six, hours. This is at least unnecessary, as with the proportions above given I always found the process completed after three hours' boiling. As a product of putrefaction, leucine may be obtained by allowing one part of cheese, flesh, or albumen, with fifty parts of water, to decompose at a temperature somewhat above 20° for about six weeks. The dirty-looking fluid is then boiled with milk of lime, the lime is precipitated by a slight excess of sulphuric acid, the filtrate is evaporated and precipitated with lead acetate, the filtrate from this is evaporated to a syrupy consistence, and the leucine which now crystallises is freed mechanically, and by the assistance of alcohol, from the syrup; it is then dissolved in water, treated with sulphuretted hydrogen, and is obtained pure by crystallisation from alcohol and water.

Leucine, $C_6H_{13}NO_2$.

Purification.—The raw leucine as obtained by the inspissation and cooling of the mother-liquors of tyrosine—freed from mother-liquor by pressure and dried—is treated with concentrated nitric acid while being triturated in a mortar, and gently heated until a slight reaction is perceived. The nitric acid solution is then diluted with much water, and a solution of nitrate of oxyde of mercury is added as long as a precipitate is thereby produced. This is removed by filtration. The filtrate is allowed to stand for some days, and separated from a new deposit. The excess of mercury is then removed by sulphuretted hydrogen; the filtrate is neutralised by ammonia, and evaporated until a pellicle forms. The leucine, which is separated on cooling, is collected on a filter, washed with concentrated alcohol, and dried. It is then dissolved in boiling water, treated with pure animal charcoal, filtered, evaporated to a pellicle, and then poured into three or four times its bulk of very strong alcohol. White leucine crystallises almost immediately and on standing. The mother-liquors yield more on evaporation, which has to be further purified by recrystallisation.

Mode of Removing all Leucine from Animal Fluids.—The fluid is treated with lead acetate, neutral and basic, the filtrate freed

from lead by hydrothion, and boiled. Copper sulphate is now added to the solution until a filtered sample gives a blue precipitate with caustic potash. The mixture is now boiled with baryum carbonate until a filtered sample is free from sulphuric acid and filtered. On evaporation of the blue liquid to dryness all the leucine is deposited in combination with copper; the compound is very insoluble in water, and has the formula $C_{18}H_{35}Cu_2N_3O_6$.

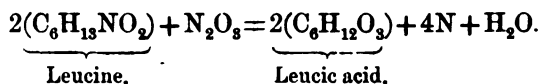
Physical and Chemical Properties of Leucine.—The sublimate of pure dry leucine appears under the microscope in strings of rhombic plates. Owing to the thinness of the scales it is of very light specific weight, perfectly white, and of great splendour. When crystallised from an alcoholic solution it represents white scales of the lustre of mother of pearl, much like cholesterine, floating on water, and imparting the sensation of an unctuous matter to the finger. When deposited from weak spirit it has the appearance of minute larch fungi, to which it was compared by Proust. In the liver and the extract therefrom it crystallises in balls, with a radiary arrangement of particles. Its shape alone can never be relied upon for diagnosis, but this must be secured by the totality of its tests.

It dissolves in 27 parts of water at the ordinary temperature of the air, and in 658 parts of alcohol of 75 per cent., or in 1040 parts of alcohol of 96 per cent., at the ordinary temperature, and in 800 parts of such alcohol at the boiling heat. It is insoluble in ether even when boiling. The presence of acetic acid and of potassium acetate increases its solubility in alcohol and water. When heated cautiously in a glass tube open at both ends it is, without previously melting, completely volatilised in the form of thick, white fumes, which resemble the white oxide rising from burning zinc. When heated suddenly in a closed vessel it fuses, emits vapours of amylamine, and leaves a mass of charcoal. It is easily soluble in dilute acids, and forms combinations, assuming readily a crystalline form. It is also easily soluble in caustic potash and ammonia.

Decompositions.—When fused with caustic potash it is decomposed into valerianate and cyanide of potassium and water, free hydrogen escaping—

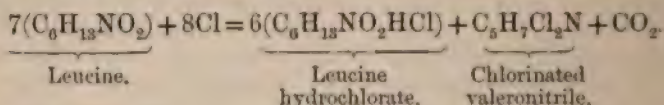


Under the influence of nitrous acid, leucine is transformed into leucic acid, nitrogen escaping—



When heated to 230° in a flask placed in an oil-bath, while a slow current of dry hydrochloric acid gas passes through, it loses an atom of water, and is transformed into *leucimide*, $C_6H_{11}NO$.

When its watery solution is treated with chlorine gas, valeronitrile, and dichloro-valeronitrile are formed, and evolved on heating, while leucine hydrochlorate remains in solution—



With manganese peroxyde and dilute sulphuric acid it yields valeronitrile on heating. On distillation with lead peroxyde and water it gives ammonia, butyric aldehyde, and carbonic anhydride. Its solution in potash is decomposed by potassium permanganate at the ordinary temperature, ammonia being evolved, and valerianic and oxalic acids remaining in combination with the base.

Combinations.—The watery solution of leucine is not precipitated directly by salts of metals with mineral acids, not even by the nitrates of the oxyde and suboxyde of mercury, nor by corrosive sublimate. But when it is boiled or evaporated with certain chlorides or acetates it drives out the whole of the acids, and forms insoluble compounds with the metals.

Leucine hydrochlorate, $C_6H_{13}NO_2HCl$, forms crystals easily soluble in water. When its solution is saturated with copper hydroxyde while boiling, and evaporated, there is formed at first dicupric trileucine, $C_{18}H_{35}Cu_2N_3O_6$, afterwards hydrated monocupric dileucine, $C_{12}H_{26}CuN_2O_6$. On repeated evaporation to dryness the whole of the hydrochloric acid is driven out, and all leucine is in combination with copper.

Leucine Nitrate, $C_6H_{13}NO_3HNO_3$, appears in colourless concentric groups of needles. It forms a salt with calcium, crystallising in small warts, and containing water of crystallisation; a salt with magnesium appearing in small granular crystals, and with other metals, and these give double salts with other salts. The nitrate of silver leucine can be produced directly by mixing and evaporating in vacuo equivalents of these substances.

Monocupric dileucine, $C_{12}H_{24}CuN_2O_4$.—On adding to a concentrated hot solution of leucine kept on the steam-bath a saturated solution of copper acetate, the fluid becomes for a moment deep blue, and then deposits a light granular precipitate. This increases by stirring, and the fluid is decolorised. The washed and dried precipitate is a beautiful sky-blue powder, with no particular lustre, and contains 19·6 per cent. of Cu. The same compound, perhaps monohydrated, is obtained by dissolving

copper hydroxyde in a leucine solution, and by evaporating a solution of copper hydroxyde in a solution of leucine hydrochlorate.

Dicupric Trileucine, $C_{18}H_{36}Cu_2N_3O_6$, is obtained by adding to a solution of leucine copper sulphate in excess, and then boiling this solution with baryum carbonate. The blue filtrate on evaporation deposits this very insoluble compound in blue scales containing 24.58 per cent. of Cu.

The Neutral Mercury Salt, $C_{12}H_{24}HgN_2O_4$, is made by dissolving such a quantity of freshly precipitated mercury oxyde in a hot solution of leucine that on cooling a turbidity ensues in the fluid. On evaporation the above salt is deposited. It is a yellowish powder, and contains 43.47 per cent. Hg.

A Basic Mercury Salt, $C_{12}H_{24}HgN_2O_4 + HgO$, is obtained by gently heating a mixture of a solution of leucine and a concentrated neutral solution of mercury acetate. It contains 59.17 per cent. of Hg.

Leucine Lead, $C_{12}H_{24}PbN_2O_4$, is obtained by adding to a boiling mixture of leucine and lead acetate cautiously a little ammonia. On cooling the fluid fills with the very insoluble compound.

Chemical Constitution.—Leucine is amido-caproic acid, that is to say, caproic acid in which an atom of hydrogen is replaced by amidogen, $C_6H_{11}(H_2N)O_2$. The nitrogen is easily removed by nitrous acid, which produces oxycaproic, *i.e.*, leucic acid, $C_6H_{12}O_3$, being caproic acid in which an atom of hydrogen is replaced by hydroxyle, $C_6H_{12}(HO)O_2$. Thus leucine is homologous to glykokoll, alanine, and butalanine, as leucic acid is homologous to glykolic, lactic, and oxybutyric acids. This conception of the constitution of leucine is further supported by its synthesis, which is effected like that of the homologous amido-acids, by boiling together the ammonia compound of valerianic aldehyde, hydrocyanic and hydrochloric acid. Leucine hydrochlorate crystallises.

Tyrosine, $C_9H_{11}NO_3$.

The tyrosine obtained as above described is purified by solution in hydrochloric acid, boiling with animal charcoal, and precipitation from the filtrate by sodium acetate. It is further purified by crystallisation from ammonia.

Physical and Chemical Properties.—It crystallises in voluminous white needles, which may be compressed to a silky felt of white colour and some lustre. It is without taste or odour. In cold water it is scarcely soluble, easily in boiling water; it is insoluble in alcohol and ether. It dissolves rapidly in mineral acids and alkalies, yielding compounds which are even soluble in alcohol. From a solution in ammonia it crystallises unchanged,

but in larger crystals on spontaneous evaporation of the fluid. From the alkaline solution it is precipitated by acids.

Decompositions, Substitutions, and Metamorphoses.—Heated on platinum foil it emits an agreeable aromatic odour, and burns without leaving any residue. (When it gives out the odour of burnt horn it is impure.)

Under the influence of nitric acid it yields at first yellow crystals of nitrate of nitrotyrosine, $C_9H_9(NO_2)NO_3 \cdot HNO_3$. Nitrotyrosine combines with other acids and with metals. By the further influence of nitric acid upon nitrotyrosine a product of oxydation without any further substitution, nitrotyrosic acid, $C_9H_9(NO_2)NO_6$, is obtained, of which the calcium salt is $C_9H_7Ca(NO_2)NO_3 \cdot 3H_2O$. This acid, by the continued influence of boiling nitric acid, ultimately yields large quantities of oxalic acid, and but small quantities of collateral products.

Under the influence of a limited quantity of potassium dichromate and dilute sulphuric acid, tyrosine is transformed into an acid highly charged with oxygen, which remains combined with chromic oxide and water. It has the formula $C_9H_{11}NO_{12}Cr_2O_3 \cdot 3H_2O$. On being heated this compound gives out water and carbonic acid, and the air being excluded leaves a pyrophorous, which ignites spontaneously on subsequent exposure, and leaves green chromic oxide. With excess of the chromic acid solution tyrosine is completely destroyed, carbonic acid alone being apparently produced.

When a solution of tyrosine in hot water is mixed with mercuric nitrate and mercurous nitrite, a crimson precipitate speedily forms, and the fluid remains of a pale red colour. The compound has the formula $C_9H_9(NO_2)_2NO_3 \cdot Hg_2$, and contains 60 per cent. of Hg. In this reaction the mercurous nitrite furnishes the nitrous acid which substitutes two atoms of hydrogen, and these latter are oxydised to water by oxygen abstracted from mercuric oxide which disappears from the solution. A mixture of mercuric nitrate and mercurous nitrite is the most delicate test for tyrosine; with a very dilute solution it yet produces a rose colour without any precipitate.

When tyrosine is treated with fuming sulphuric acid, allowed to stand for half an hour, diluted with water, neutralised with calcium carbonate, and filtered, then, on addition to the filtrate of a solution of iron chloride containing no free acid, a rich violet colour is immediately produced. The reaction consists in the formation of sulpho-tyrosinic acid, of which all neutral salts give the same coloration with neutral iron chloride.

Compounds with Metals.—Tyrosine forms two series of compounds with metals, in which either one or two atoms of hydrogen are replaced. Thus with baryum it yields $C_9H_7BaNO_3 + 2H_2O$ and $C_{18}H_{20}BaN_2O_6$; with silver it gives

$C_9H_9Ag_2NO_3 + H_2O$ and $2(C_9H_{10}AgNO_3) + H_2O$. These compounds are not very stable.

Compounds with Acids.—Tyrosine hydrochlorate forms when to a solution of tyrosine in the acid an excess of strong hydrochloric acid is given. The hard crystals are decomposed by water. The nitrate, $C_9H_{11}NO_5HNO_3$, and the sulphate, $C_9H_{11}NO_5H_2SO_4$, both crystallise, but are decomposed by water.

Chemical Constitution.—From the whole of the data concerning tyrosine it is clear that the nitrogen contained in it does not exist either in the nitro state, nor as amidogen or imidogen. Iodide of ethyl effects no substitution. Therefore the nitrogen must be altogether in direct combination with the carbon. There is no hydroxyl, otherwise hydriodic acid would effect a reduction. Therefore all the oxygen must be in direct and complete union with carbon. There is certainly no sign of highly condensed oxygen in tyrosine. It seems to be derived from C_9H_{20} , being the fully expanded hydride of nonyl, which has undergone substitution to a considerable extent, three atoms of hydrogen having been replaced by a tridynamic atom of nitrogen, N''' , and six atoms of hydrogen by three atoms of oxygen. Tyrosine is volatile, without decomposition, in a nearly vacuous space. At one pole of its molecule there will exist N''' , at the other pole COH , thus: $N'''CCH_2CH_2CH_2CH_2CH_2COCOC \begin{Bmatrix} O \\ H \end{Bmatrix}$.

The great stability of tyrosine is a sign that the grouping of its carbon is regular. Everything in its chemical history converges towards this rational formula.

The fact that with dilute chromic acid it gives no acetic acid negatives the assumption of there being ethyl in union with part of the nitrogen, or in union with oxygen. The easy formation of carbonic acid is in harmony with the existence of the three atoms of carbonic oxyde. The non-production of picric acid by oxydation with nitric acid is significant of the non-existence of the aromatic group.

So remarkable a substance was well designed to form the nucleus of the albuminous substances. Oxydisable without remnant, it is always entirely destroyed by biolysis, and not found in the healthy economy; product of patholysis and chemolysis, it presupposes the lowering or absence of oxydising power which in these processes we find or engender. The stability of tyrosine makes it a fit starting-point for the synthesis of the album substances, which we may expect to see ere long effected.

Pathological Indications of Leucine and Tyrosine in the

The presence of these substances in the urine is of a disease which by some is considered as typhoid of the liver, by others as a specific disorder having

with the typhus process. As in the majority of cases the liver is greatly diminished in size and of a yellow colour, the disease has received the name of acute yellow atrophy of the liver. But as there are undoubtedly cases in which the liver is greatly increased in bulk, the foregoing name is not sufficiently comprehensive, and should yield to a better description. As the disease is always acute, mostly fatal, and invariably accompanied with jaundice, it is best described as *acute malignant jaundice*. The disorder generally begins with the symptoms of gastric derangement, vomiting of mucous matters, ultimately containing blood altered to a black matter by the influence of the gastric juice and jaundice more or less prolonged. The brain then becomes involved, and the patients either pass through violent headache into a delirious state, or sink early into coma, from which they can only be roused by loud calling. In some cases convulsions follow the delirious state, and affect either the whole or part only of the voluntary muscles. Ultimately the patients sink into deep coma; the pulse, which during the early stages of the jaundice was slow, becomes quick during the delirium, rising to 110 and 120, and then changes quickly and often. Towards the end of the process it becomes very quick, and can no longer be felt at the wrist. There is mostly pain in the hypochondriac regions, aggravated by pressure, particularly in the region of the liver. The size of this organ is mostly diminished, sometimes, however, increased. The spleen is increased in size. The intestines are torpid, the feces dry and pale, or if dark and fluid, mixed with altered blood. The skin becomes more intensely jaundiced as the process is developed, and shows petechiæ and extravasations. The urine is mostly at first but little diminished in quantity; during the comatose period it has to be collected by means of the catheter, as otherwise it is passed involuntarily. It is always acid, its specific gravity ranges from 1012 to 1024; during the progress of the jaundice its colour passes from amber to dark brown, and nitric acid then yields the reaction for cholechrome. It makes a deposit on standing which in the early febrile stages may contain urates. Later the deposit contains no urates, but consists of desquamated epithelium of the urinary passages and kidney tubes, mixed with a number of crystalline needles lying singly or united in groups, being tyrosine dyed with altered biliary pigment. The urine rarely contains albumen. Phosphoric acid and calcium gradually disappear entirely. The urea becomes diminished, and disappears at last completely, its place being apparently taken by tyrosine, large quantities of leucine, ammonia, and peculiar amorphous matters which have been termed extractives, but not otherwise defined or distinguished from the normal so-called extractives of the urine.

Clinical Analysis of the Urine.—After the microscopic

examination of the urine the deposit is collected on the filter, and extracted with dilute ammonia. This solution will contain all tyrosine of the sediment, and deposit it in needles on spontaneous or gentle evaporation in a dial-plate or watch-glass. On evaporation and cooling the urine will deposit more tyrosine, which is purified like the spontaneous deposit. The urine is then again diluted and treated with acetate of lead, next with basic acetate, and after removal of the precipitates freed from excess of lead by hydrothion. The filtrate, which is free from normal and abnormal colouring matters, kryptophanic, sulphuric, and phosphoric acids, is evaporated to a syrupy consistence. It then mostly deposits leucine in the usual granules, mixed with tyrosine. But sometimes the syrup refuses to crystallise, and has to be digested with cold absolute alcohol, which dissolves the syrupy matters. The residue is then treated with boiling spirit of wine, which extracts, and on cooling deposits the leucine in a crystalline form. It leaves a syrupy matter undissolved, very much resembling the brown viscid syrup which is obtained during the process of preparing leucine and tyrosine from albuminous substances by the process above described. The solution in cold alcohol may contain urea and leucine. On addition of a quantity of ether, amounting to from one-half to an equal volume, it deposits an amorphous matter, from which leucine is gradually separated in crystals. The ether and alcohol solution retains any urea and ammonium salt which may be present. The ether is removed by distillation, and to the alcoholic residue a solution of oxalic acid in alcohol is given. Any precipitate which ensues may be either urea or ammonium oxalate. This is decomposed with calcium carbonate. The filtrate will yield any urea on evaporation and addition of nitric acid; while ammonia will evaporate as carbonate during the treatment with chalk, and must be collected if it be desirable by conducting the process of decomposition in a retort.

The processes described in the foregoing are applicable to the isolation of leucine and tyrosine from any tissue, if the latter is minced or triturated with glass powder and extracted with boiling water. Blood or serous fluids require extraction with boiling water to which acetic acid has been added until the mixture has an acid reaction. The watery extracts may then be treated like the urine. The bile in typhus is said sometimes to contain leucine. In such cases the bile may be treated with neutral and basic lead acetate to remove biliary acids, or its dry residue extracted with absolute alcohol to dissolve their salts. The residues in either case are treated like the urine above described.

CHAPTER LXI.

OXYMANDELIC ACID, $C_8H_8O_4$.

HISTORY AND OCCURRENCE.

THIS acid, so called because in its formula it contains one atom of oxygen more than the acid which figures in chemistry under the name of mandelic acid, was found by Schultzen and Riess ("Ann. d. Chariték." Berlin (1869), 15, 72) in several cases of malignant jaundice in the urine, together with leucine, tyrosine, sarcolactic acid, biliary acids, and pigments, small quantities of albumen and a peptone-like substance which appears in urine frequently and in large quantity after acute poisoning with phosphorus. The urea was either entirely absent or reduced to a minimum. Leucine and tyrosine were never absent.

Mode of Isolating it from Urine.

The urine is evaporated, and the leucine and tyrosine, which are deposited, are removed; the mother-liquor is precipitated with absolute alcohol; the alcoholic solution is evaporated, and the syrupy residue, after acidulation with dilute sulphuric acid, is exhausted with ether. The ether extracts after distillation leave a brown fluid residue, from which long, thin, colourless needles, besides brown oily drops, are deposited. The needles are dissolved in water; in the yellowish filtrate neutral lead acetate produces a slight flaky precipitate, whereby the fluid becomes less coloured. The clear filtrate now gives with basic lead acetate immediately a flaky precipitate, which after some standing is condensed so as to form a heavy, granular, crystalline powder. This is suspended in water and decomposed by hydrothion. The filtrate, after evaporation, yields colourless, silky, flexible needles of oxymandelic acid.

Physical and Chemical Characters.

The acid contains 4.6 per cent. water of crystallisation, which escapes in part on exposure to air, but is completely expelled at 130° ; it fuses at 162° . It is little soluble in cold, easily soluble in hot water, in alcohol, and in ether. On being heated in a glass tube with hydrate of lime, brown oily drops are evolved

which smell of phenol, and in contact with a watery solution of ferric chloride give a dark violet colour. The calcium salt of the acid $(C_8H_7O_4)_2Ca + 2H_2O$, crystallises in colourless glass-like needles.

New Nitrogenised Acid in Phosphorus Poisoning.

From a specimen of urine which came from a case of acute poisoning by phosphorus, Schultzen and Riess obtained an alcohol and ether extract, and from this a syrup which deposited warts of colourless rhombic scales. They constituted a nitrogenised acid, which was not precipitated by basic lead acetate, but by silver nitrate. The argentic precipitate crystallised from boiling water in shining white needles, and contained 33.9 per cent. Ag. The acid was decomposed by heat, and on distillation with lime gave aniline. It fused at 184° to 185° .

CHAPTER LXII.

KYNURIC ACID, $C_{20}H_{14}N_2O_6$, $2(H_2O)$.

HISTORY AND LITERATURE.

THIS acid was discovered by Liebig in the urine of dogs, of which it is a normal constituent. He estimated the composition of the acid to be expressed approximatively by the formula $C_{16}H_{14}N_2O_5$. Schneider was the first to analyse some salts, and from the baryum compound estimated the formula to be $C_{20}H_{18}N_2O_6$. The acid was then examined by Schmiedeberg and Schultzen ("Ann. Chem." 164 (1872), 155), who came to the formula adopted in the heading.

Mode of Obtaining.

The urine of dogs is mixed with some hydrochloric acid, and allowed to stand for some days. After that time the acid is found deposited in dark coloured, almost black, little scales, mixed not unfrequently with a little uric acid, and some free sulphur. From the latter the acid is separated by levigation, from the uric acid by solution in ammonia and filtration. If the urine should be very dilute, or contain little acid, it may be necessary to evaporate it to one-third, precipitate with neutral lead acetate, remove excess of lead by hydrothion, and add hydrochloric acid.

The crude dark kynuric acid is purified by repeated solution in ammonia, treatment with animal charcoal, and precipitation of the hot diluted solution with acetic acid. The kynuric acid is then deposited in large scaly crystals, which, grey at first, after complete purification become pearly white.

Physical and Chemical Properties.

The composition of the acid is expressed by the formula $C_{20}H_{14}N_2O_6 + 2H_2O$, or perhaps half that formula. The two molecules of water are expelled by heat at 150° . The acid is almost insoluble in either hot or cold water, containing a little hydrochloric or nitric acid, but is easily soluble in concentrated acids. It is somewhat soluble in hot alcohol, and on cooling is partially deposited in fine needles. In ether it is slightly

soluble. At 264° to 266° it fuses, gives out carbonic acid gas, and is transformed into a brown liquid, which congeals slowly. This residue can be recrystallised from hot water, purified by animal charcoal, and then crystallises in groups of glass-like prisms, which are very insoluble in water. They are anhydrous, permanent in air, fuse at 201° , neutral, soluble in alcohol, combine with hydrochloric acid to form a crystallised salt, which combines with platonic and auric chloride to very definite double salts. The free base, kynurine, has the composition expressed by the formula $C_{18}H_{14}N_2O_2$; the hydrochlorate, $C_{18}H_{14}N_2O_2 + 2(HCl) + H_2O$; and the platinum salt, $C_{18}H_{14}N_2O_2 + 2(HCl) + PtCl_4$. Kynurine is derived from kynuric acid according to the equation—



When kynuric acid is heated to 180° , with hydriodic acid in a sealed tube, prisms of a new body are obtained.

With baryum the acid forms a crystallised salt, of the formula $C_{20}H_{12}N_2O_6Ba + 3(H_2O)$ (26.70 per cent. Ba), which is little soluble in hot, almost insoluble in cold, water. Excess of baryta water dissolves the salt very easily. The crystals lose their water of crystallisation only at 150° to 160° . No other baryum salt of kynuric acid is known, and the acid might therefore also be assumed to be monobasic, and to have the formula $C_{10}H_7NO_3$. But the formation of kynurine caused Schmiedeberg and Schultzen to double the formula. I do, however, not see the cogency of their argument, inasmuch as the formulæ of kynurine and its salts can be written quite as well, if not with better regard to probability, with the aid of the formula C_9H_7NO .

CHAPTER LXIII.

UROCANINIC ACID, $C_{12}H_{12}N_4O_4$.

HISTORY AND LITERATURE.

THIS body was found in the urine of a dog by Jaffé ("Ber. Deutsch. Chem. Ges." 7, 1669, and 8, 811). The dog ran away, and then the excretion of eight different dogs was examined, but none yielded the new substance. It is therefore, if not a pathological, at least an anomalous ingredient of the excretion. It may be recorded as a warning to be heeded in similar circumstances, that Jaffé observed the new principle first in the dog's urine after he had given it paranitrotoluol to eat, and believed it to stand in some relation to that circumstance. But three months after this, when the dog was taking ordinary food and no paranitrotoluol, and was apparently perfectly healthy, it still excreted the new acid.

Mode of Obtaining.

The urine was evaporated to a syrup on the water-bath, and repeatedly extracted with hot alcohol. The alcohol was distilled from the extracts, the residue acidified with dilute sulphuric acid, and extracted with ether. After removal of the ether the residue formed a paste of crystals, which were freed from mother-liquor on the vacuum filter, washed with little water, freed from urea by alcohol, and obtained pure by recrystallisation.

These crystals were a sulphate of the new body. The sulphuric acid was removed by cautious addition of baryta water, and filtration while hot. An excess of baryta water had to be avoided, as it formed an easily soluble, non-crystallising, baryum salt with the acid. Or the sulphate was dissolved in ammonia, and precipitated by acetic acid. The precipitate recrystallised from water yielded the substance pure.

Physical and Chemical Characters.

Urocaninic acid crystallises in long, colourless, thin prisms, or in needles. It contains water of crystallisation, which goes away at 105° . It is very little soluble in cold water, easily in hot water, insoluble in alcohol and in ether. It can be heated to

near its fusing point without undergoing decomposition, but it fuses at 212° to 213° , with evolution of carbonic acid and water to a yellowish oil, which on cooling sets to a glassy mass. This is mainly a new base, *urocanine*, and its formation occurs according to the equation $C_{12}H_{12}N_4O_4 = C_{11}H_{10}N_4O + CO_2 + H_2O$.

The base is soluble in alcohol, but does not crystallise from it. It is somewhat soluble in hot water, and the solution on cooling becomes turbid, and deposits flakes. It forms salts with acids which do not crystallise. In the hydrochlorate, platinic chloride produces a precipitate which is at first amorphous, later crystalline, and has the formula $C_{11}H_{10}N_4O \cdot 2HCl \cdot PtCl_4$. It is little soluble in cold water, fuses in hot water to a reddish-brown oil, and is very hygroscopic, insoluble in alcohol and in ether.

Urocaninic acid has the combining faculties of an acid and of a base at the same time. In the latter quality it combines with mineral acids, forming crystallised salts, but it does not combine with acetic or oxalic acid.

The hydrochlorate, $C_{12}H_{12}N_4O_4 \cdot 2HCl$, crystallises from hot, concentrated, hydrochloric acid in needles, easily soluble in water.

The nitrate, $C_{12}H_{12}N_4O_4 \cdot 2HNO_3$, is obtained as a crystalline precipitate by adding nitric acid to a watery solution of urocaninic acid. The salt is almost insoluble in dilute nitric acid, and in alcohol, but easily soluble in water. The crystals must be washed with dilute nitric acid, and dried in vacuo over caustic potash. They may then be heated to 110° without decomposition.

The sulphate, $C_{12}H_{12}N_4O_4 \cdot H_2SO_4$, crystallises from hot dilute sulphuric acid in microscopic needles and scales. It is like the nitrate, anhydrous, little soluble in cold water and in alcohol, insoluble in absolute alcohol.

CHAPTER LXIV.

LITHURIC ACID, $C_{15}H_{19}NO_9$.

HISTORY AND LITERATURE.

A VETERINARIAN at Pietrasanta, in Tuscany, some years ago observed that oxen which were used for tilling the soil excreted from time to time roundish concretions, which differed in appearance from commoner forms. He collected some and sent them through the mediation of the local physician, Linoli, to the laboratory for pathological chemistry at Florence, where they were analysed by Roster, with the following results ("Ann. Chem." 165 (1873), 104).

Physical and Chemical Characters of the Concretion.

The largest calculus obtained weighed 1.02 gm., was 25 m.m. long, and 8 m.m. thick; the smallest weighed 0.15 gm., and was 6 m.m. long, and 5 m.m. thick. They were of low specific gravity, but did not float on water. Their colour was light straw yellow, sometimes with an admixture of grey. On fractures layers were not observed, but a clearly crystalline structure. They could not be disintegrated by pressure between the fingers, but easily powdered in a mortar. The powder, or smaller fragments, when inspected by the aid of the microscope exhibited transparent prisms of greater or shorter length and diameter, the ends of which were terminated by two planes, similar to the ends of crystals of hippuric acid. They consisted almost entirely of the magnesium salt of a nitrogenised organic acid, which was soluble in hot water. Besides this they contained only a trace of calcic carbonate and some mucous matter. The solution in boiling water was filtered, and on cooling deposited a white, silky, crystalline precipitate.

Physical and Chemical Characters of the Purified Salt and the Free Acid.

The pure substance, as obtained by repeated crystallisation, appears in transparent clinorhombic prisms, with two planes pointing each end. More rarely it crystallises in thin needles.

It can be washed with cold water, in which it is very little soluble.

It is insoluble in alcohol and ether. Heated on platinum it blackens, fuses, and then burns almost without flame, giving out the smell of burning sugar. On heating with soda lime it evolves ammonia, but not on boiling with caustic potash solution. It contains no sulphur. It leaves an ash consisting of magnesia only. From the elementary analyses Roster calculates the formula $C_{25}H_{36}N_2MgO_{17}$, or $C_{30}H_{36}N_2MgO_{18}$, for the salt.

On adding to the hot saturated watery solution of the salt some hydrochloric acid, and allowing the mixture to stand and cool, white silky needles of lithuric acid are deposited. They fuse at first at 200° , but after several recrystallisations the fusing point rises to 203° and 204.5° . The formula of the acid, as deduced from the magnesium salt, is probably $C_{15}H_{19}NO_9$.

CHAPTER LXV.

DAMALURIC AND DAMOLIC ACID.

HISTORY AND OCCURRENCE.

THESE volatile acids were discovered by Städeler ("Ann. Chem." 77 (1851), 17), and as far as I am aware have not yet been studied any further by other observers. The material from which he originally obtained them, together with phenol and cresol (taurylic acid), was the urine of cows, and later that of horses. But he says (p. 34) that he also, in one experiment with three pounds of human urine, found both groups of acids, upon which Liebig, as the then editor of the "Annalen," referred to his own researches in vol. 50, 172, in the course of which he had again proved the presence of acetic acid in (putrid) urine. As we know from a former chapter that human urine, both fresh and fermented, yields large quantities of acetic and formic acid, it is surprising that these acids are not mentioned by Städeler. This circumstance makes his statement regarding the presence of damaluric and damolic acid in human urine extremely doubtful.

Mode of Obtaining.

Eighty pounds of fresh morning urine of cows, which during the daytime were grazing, but in the morning and evening had a feed of hay, straw, and bran, was mixed with milk of lime, boiled up, decanted from the excess of lime, and evaporated at boiling heat to about one-eighth of its volume. The filtrate was then well cooled, mixed with hydrochloric acid until it showed a strongly acid reaction, and after twelve hours' standing separated from the deposit of hippuric acid. This mother-liquor yielded on distillation a milky, strongly-smelling fluid, which deposited a few viscid yellow or greenish oily drops. The distillate was repeatedly rectified, and ultimately there was obtained an oily, pale yellowish liquid, settled below the water, which had simultaneously passed over. This oil, together with the watery distillate, was mixed with a weighed quantity of potassic hydrate until it had a strongly alkaline reaction, and again distilled; a pale yellow *light oil* of penetrating odour was obtained as distillate. Städeler supposes this light oil to be a

product of the action of the potash upon one of the most odorous ingredients of the main distillate. It was distilled over dilute sulphuric acid, and became perfectly neutral. On being heated with soda lime it evolved much ammonia, and in oil of vitriol it dissolved with a deep wine red colour, which became gradually paler and colourless on addition of water. This nitrogenated oil was not any further examined, as the quantity obtained was too small.

The alkaline solution from which this light oil had been separated was now treated as follows, in order to separate the hydrochloric and benzoic acid which it contained:—Five-sixths of the potassic hydrate employed were saturated with sulphuric acid, and the mixture was then distilled until the distillate did not any longer give a precipitate with basic lead acetate. The entire distillate, which had the odour of phenylic acid, was repeatedly rectified over sodic chloride, until the greater part of the acids was obtained in an oily form, with only a small portion of a watery solution. Water solution and oil had a strongly acid reaction, and were saturated with sodic carbonate, and frequently shaken during twelve hours. The oily layer had been much diminished by this treatment, and was separated by means of ether from the sodium salts.

Acids which did not Decompose Sodic Carbonate.

The ether solution was distilled, and the residue further distilled with concentrated potash ley. A small portion of the indifferent nitrogenised light oil above described passed over. The alkaline residue was decomposed with potassic bicarbonate, and distilled; the distillate, which weighed about 25 grm., was left for some time in contact with fused calcic chloride, and then rectified over calcic chloride. The distillate on fractional distillation gave much phenol, which passed over at 180° to 195° , but was still somewhat impure, containing some of the light nitrogenised oil, so as to yield 0.63 per cent. nitrogen on analysis, and some of the homologous *taurylic acid* or *cresol*, $C_7H_8O_2$. The presence of this latter body was made probable by the higher boiling point, and the excess of carbon and hydrogen obtained in the elementary analyses of the phenol. It further yielded a characteristic compound with sulphuric acid, which crystallised quickly in tender white ramified masses, while phenol, when combined with sulphuric acid, yielded a compound which remained fluid for months. This crystallised compound, however, was so hygroscopic, that when Städeler placed it upon a slab of plaster of Paris to remove the adhering sulphuric and phenol sulphuric acid, it became liquid, and disappeared in the plaster.

Acids which Decomposed Sodie Carbonate.

The solution of potash salts, which had been freed from the phenol and cresol just described by ether, was evaporated to remove ether, and then decomposed with sulphuric acid, and distilled. The distillate, which had a peculiar odour reminding of butyric acid, separated into two layers; the lower one was a colourless, heavy, oily liquid, the upper one was a solution of these acids in water, and strongly reddened litmus. The watery solution was boiled with barytic carbonate, and the alkaline solution was evaporated. After twenty-four hours flat, shiny prisms formed; the mother-liquor in the vacuum over sulphuric acid had deposited a second set of crystals which were not analysed. A third and fourth quantity of crystallised matter were obtained:—

1st crystals,	fusible,	contained 27.46 per cent. BaO.
2d	"	not analysed.
3d	"	infusible, contained 39.36 per cent. BaO.
4th	"	fusible, " 44.46 " "

The oily part of the acids was now also transformed into baryum salts, and yielded on fractional crystallisation six preparations, with the following percentages of baryum oxyde:—

1st crystals	}	fusible	{	contained 27.50 per cent. BaO.		
2d				"	27.85	" "
3d	}	infusible	{	"	39.03	" "
4th				"	39.18	" "
5th				"	...	" "
6th, the evaporated mother-liquor				41.00	"	" "

The main quantity of salts were those with a little more than 39 per cent. of baryum oxyde. Further analysis showed that this salt contained a new acid, to which Städelcr gave the name of

Damaluric Acid.

It had a peculiar odour, not unlike valerianic acid, was a little heavier than water, and formed with basic lead acetate a white precipitate, which under the microscope consisted of fine prisms united to balls. Its elementary composition is expressed by the formula $C_7H_{12}O_2$. The baryum salt requires by theory 39.18 per cent. BaO, which is well supported by the quantities found. A silver salt produced by precipitating the solution of the baryum salt with argentic nitrate gave on analysis numbers which corresponded accurately with the formula $C_7H_{11}AgO_2$.

Damolic Acid.

This acid, which as regards quantity follows next to damaluric acid in the mixture, is the one whose baryum salt is the first to

crystallise from the solution of the mixed salts, and is distinguished by its fusibility from the infusible barytic damalurate. The salt contained in the mean 27.63 per cent. baryum oxyde; its solution had an alkaline reaction, and it cannot, therefore, be an acid salt. The acid is separated from the baryta by hydrochloric acid in heavy oily drops, which do not solidify. It cannot therefore belong to the series of fatty acids, of which those of similar atomic weight are solid.

Acids of the Salts with above 40 per cent. Baryum Oxyde.

The salts were considered by Städeler as mixtures of baryum damalurate with another baryum salt. But he could not decide whether the second acid in these salts was butyric, valerianic, or an unknown acid.

Form in which these Acids are probably contained in the Urine of Cows.

When Städeler simply distilled cows' urine without any reagents, he obtained only an ammoniacal, disagreeably smelling distillate, without any phenol or damaluric acid. But when he evaporated such urine at a low heat to one-eighth, after cooling added sulphuric acid, removed the hippuric acid precipitated on standing, and extracted the dark brown liquid with ether, he obtained in the residue from the ether some cresol and phenol, and traces of damaluric and damolic acid. He therefore concluded that these bodies were present in the urine ready formed, but combined with alkalies. These views should be compared with what I have stated under the chapters referring to phenol and cresol producing bodies. As regards damaluric acid he believed that at least a portion might be a product of the cleavage, under the influence of caustic potash, of the odoriferous ingredient of the urine employed; and that the second product of this cleavage might be the nitrogenised neutral light oil described above.

Städeler did not estimate the volatile products quantitatively, but believed their relative quantities to observe the following order:—Cresol (taurylic acid) was present in largest amount; next came phenol, and damaluric acid; damolic acid scarcely amounted to one-quarter of the weight of the damaluric; and in smallest quantity was present the acid, the baryum salt of which contained more than 40 per cent. of baryum oxyde.

CHAPTER LXVI.

UROPHANIC ORGANIC ACIDS.

INTRODUCTORY REMARKS.

- | | | | | | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-------------------|-----------------------------------------------------------------------------------|---|-----------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> 1. Succinic acid. 2. Tartaric acid. 3. Gallic and pyrogallie acid. 4. Toluic acid. 5. Salicyluric acid. 6. Salicylous acid. 7. Meconic acid. 8. Camphoric acid. 9. Anisic acid. 10. Cuminic acid. 11. Abietinic acid. | <table style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td style="vertical-align: top;"> <ol style="list-style-type: none"> 12. Benzoic acid, 13. Benzoic ether, 14. Oil of bitter almonds, 15. Cinnamic acid, 16. Chinic acid, 17. Mandelic acid, 18. Nitro-benzoic </td> <td style="vertical-align: middle; font-size: 3em; padding: 0 10px;">}</td> <td style="vertical-align: middle;"> give
hippuric. </td> </tr> <tr> <td style="vertical-align: top;"> <ol style="list-style-type: none"> 19. Citric, 20. Malic, </td> <td style="vertical-align: middle; font-size: 3em; padding: 0 10px;">}</td> <td style="vertical-align: middle;"> and their salts, when
taken even in large
doses, do not reappear
in the urine. </td> </tr> </tbody> </table> | <ol style="list-style-type: none"> 12. Benzoic acid, 13. Benzoic ether, 14. Oil of bitter almonds, 15. Cinnamic acid, 16. Chinic acid, 17. Mandelic acid, 18. Nitro-benzoic | } | give
hippuric. | <ol style="list-style-type: none"> 19. Citric, 20. Malic, | } | and their salts, when
taken even in large
doses, do not reappear
in the urine. |
| <ol style="list-style-type: none"> 12. Benzoic acid, 13. Benzoic ether, 14. Oil of bitter almonds, 15. Cinnamic acid, 16. Chinic acid, 17. Mandelic acid, 18. Nitro-benzoic | } | give
hippuric. | | | | | |
| <ol style="list-style-type: none"> 19. Citric, 20. Malic, | } | and their salts, when
taken even in large
doses, do not reappear
in the urine. | | | | | |

UNDER this head I wish to notice a series of organic acids which never appear in the urine as products of the organism, but as substances simply passing through the body without undergoing destruction. Of some acids only a small proportion reappears in the urine, after the ingestion of large doses into the stomach. The same acids when introduced in small quantities are entirely oxydised in the body, and their salts appear in the urine as the carbonates of the respective bases. Besides the acids which may be totally oxydised in the body, or of which a small proportion only may appear in the urine, we have to notice acids of which the entire amount appears either unchanged, or partially changed, or combined. Gallic acid seems to pass unchanged through the body; tannic acid is transformed into gallic and pyrogallie acid; salicylic acid, imitating benzoic acid, combines with glykokoll, and appears in the urine as salicyluric acid. The occurrence of these substances in urine is mostly accidental, and dependent upon the inspiration of some experimenter, few only being administered as medicines.

History and Literature.

The first extensive researches on the changes which substances introduced into the stomach undergo or not undergo before they reappear in the urine, were instituted by Wöhler (Tiedemann and Treviranus "*Zeitschr. für Physiologie*," 1, 125). Many

urophanic substances were investigated by Wöhler and Frerichs ("Ann. Chem." 65, 335) conjointly, and by Heller and Kletzinsky, who contributed many papers in the six volumes of Heller's "Archiv."

1. Succinic Acid, $C_4H_4O_3H_2O$.

History and Occurrence.—Meissner and Shepard ("Unters. Hippurs." Hanover, 1866) have stated that they found succinic acid in normal urine. This would not be surprising if, e.g., articles of food containing this acid were eaten, or if, as is stated by Hilger, asparagine and asparaginic acid were decomposed in the body so as to reappear as ammonia and succinic acid in the urine. But we find that Knieriem came to results differing from those of Hilger, and the results of Meissner and Shepard, as also those of Meissner and Koch ("Zeitschr. ration. Med." 24, 97, and 264), and Meissner and Joly have been questioned by E. Salkowsky (Pflüger's "Archiv." 4, 94), who could not find succinic acid in the urine of a dog fed during 30 days upon horse-flesh and pigs' lard, by a method which allowed the recovery of 0.071 out of 0.088 gm. succinic acid added to a certain quantity of urine.

Mode of Searching for Succinic Acid in Urine.—The urine (of dogs) is precipitated with baryta, the excess of the latter removed by sulphuric acid, the rest of the alkalinity is neutralised by hydrochloric acid, and the liquid evaporated. The concentrated solution is acidified with sulphuric acid and extracted with ether. The latter is distilled off; if in the residue no crystallisation of succinic acid takes place, it is warmed with very dilute nitric acid. The acid, if present, then crystallises, and is purified by pressing between paper, and recrystallisation from alcohol containing ether.

Physical and Chemical Properties.—The acid sublimes at 120° to 130° , without fusing. For fusion rapid heating to 180° to 182° in a narrow space is required. With neutral lead acetate it gives a precipitate, soluble in excess of the acetate, but falling out as a crystalline powder on warming and shaking. The solution of succinic acid, when neutralised with ammonia, and mixed with barytic chloride and spirit of wine, produces a precipitate of barytic succinate. The solution of succinic acid, boiled with excess of magnesia carbonate and filtered, gives, on the addition of some neutral ferric chloride, a voluminous, brown precipitate of ferric succinate. The ferric succinate, after washing, decomposed by excess of ammonia, filtered, and evaporated to neutrality, gives with silver solution a white precipitate of argentic succinate. The latter salt, decomposed by hydrothion, gives pure succinic acid.

Physiological Relations.—When a man takes succinate of

sodium (20 grm.) at night, he generally passes nearly half the amount of this salt with his urine during the next twenty-four hours. The rest is oxydised and, as carbonate, imparts to the urine a strongly alkaline reaction, and the faculty of effervescing with acids.

2. *Tartaric Acid*, $C_4H_6O_6$.

This acid occurs in grapes and wines in the form of acid potassium salt (tartar).

When a dog is made to eat two drachms of powdered tartaric acid, mixed with bread and meat, and the urine, which is more than usually acid but contains no albumen, is collected during from three to six hours afterwards, it will on cooling deposit a number of small white crystals, similar to calcic oxalate. By addition to the urine of some calcic nitrate another quantity of the same precipitate is obtained, which together with the first one amounts to about one-quarter of the weight of the acid given. On exposure to red heat the precipitate evolves the peculiar odour of burning tartrates, and leaves a residue of calcic carbonate mixed with some charcoal. Tartrate and bitartrate of potassium, tartrate of potassium and boracic acid, tartrate of potassium and sodium, or Seignette salt, when taken in doses from one to three drachms, make the urine alkaline. When cream of tartar has been taken, the urine contains no tartaric acid while it is alkaline, but on again becoming acid, the acid can easily be detected by adding to the urine some calcium nitrate, which will cause a precipitate of calcium tartrate to be recognised as a tartrate by the peculiar odour on burning.

Mode of Obtaining Tartaric Acid from the Human Urine after its Ingestion into the Stomach.—The urine is treated with chloride of calcium and ammonia, and the precipitate formed hereby quickly removed by filtration. It consists of phosphate of calcium, and does not contain any tartrate. The filtrate is evaporated to $\frac{1}{5}$ th or $\frac{1}{3}$ th of its bulk, and put aside for six or eight days. The precipitate which has formed after the lapse of that time is separated by filtration, washed, dissolved in dilute hydrochloric acid, which leaves the greater part of the sulphate of calcium undissolved; the solution is next neutralised with ammonia and acidulated with acetic acid until the precipitate produced by the ammonia has disappeared. After the lapse of six or eight days, the tartrate of calcium, which is very little soluble in acetic acid, has crystallised in large and small crystals. They are dried at 100° and weighed. In this manner about $\frac{1}{6}$ of the tartaric acid contained in or added to any urine can be actually recovered.

Buchheim and Piotrowsky made a number of experiments with

free tartaric acid, and neutral tartrates, and double salts, the results of which are exhibited in the following table:—

Form in which the acid was taken.	No. of Experiment.	Grm. of acid taken.	Percentage of Acid found in Urine.
$C_4H_6O_6$	I.	19·6	1·78
	II.	20·0	1·83
	III.	30·0	3·79
	IV.	30·0	3·27
	V.	10·0	1·47
	VI.	10·0	2·86
	VII.	5·0	1·89
	VIII.	2·0	...
$C_4H_2KO_6$	IX.	35·0	1·00
	X.	47·82	1·85
$C_4H_2K_2O_6$	XI.	19·88	1·63
	XII.	19·88	1·69
	XIII.	29·81	1·63
$C_4H_2KNaO_6 + 4H_2O$	XIV.	23·90	3·32
	XV.	23·90	4·68
	XVI.	31·87	5·14

Of the salt with potassium and sodium, a larger percentage appears in the urine.

Of tartaric acid, a much smaller percentage reappears in urine than of oxalic acid.

These authors also made an experiment with tartrate of iron and potassium, of which 10 grm. were taken in one dose. The strongly acid urine contained no tartaric acid, and no increased amount of iron in its ash. The whole of the iron seemed to pass away in the soft, blackish-green fæces.

Tartrate of suboxyde of nickel and potassium when given to dogs passes in part into their urine, and can be shown to be present by ammonia sulphide. When a human being takes a dilute solution of this salt, so as to introduce about 1 grm. of metallic nickel into his body, the urine only contains traces of nickel for a short time, and no tartaric acid. The nickel passes away on the second and third day in the fæces as dark brown sulphide.

3. *Gallic Acid*, $C_7H_6O_6 + H_2O$.

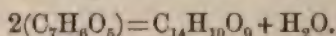
When gallic acid is taken internally, a portion at all events appears in the urine unchanged. No experiments have as yet been made regarding the quantity which is again excreted. A small part seems to be transformed into pyrogallic acid. When to a dog pure tannic acid, in doses gradually increasing from 0·5 to 6·0 grm. is given, the animal remains well, but the fæces gradually cease to be discharged, though the appetite remains

the same. The urine, in the beginning of the experiment, shows the normal yellow colour, which, however, gradually changes into a dark, lastly intensely brown colour, until at last it becomes brownish-black, and impervious to transmitted light.

The brown urine yields a blackish-blue precipitate with salts of oxyde of iron, but no precipitate is produced in it by a solution of gelatine. Tannic acid, consequently, in its transit through the body, has become transmuted into gallic acid.

Salts of the suboxyde of iron produce a bluish-black precipitate in the urine, indicating the presence of pyrogallallic acid. As this acid, in presence of ammonia, is easily transformed into humine-like bodies, it is reasonable to explain the black colour of the urine by the further decomposition of the pyrogallallic acid, for which the ammoniacal condition of the urine affords the opportunity. The dark colour and peculiar reactions of the urine continue for two days after tannic acid has ceased to be administered.

By the action of acids, alkalies, or ferments, tannic acid, taking up water, is transformed into gallic acid. Tannic acid is, according to Schiff ("Ann. Chem." 170, (1873) 43, and 175 (1875), 165), the ethereal anhydride of gallic acid, or it is digallic acid in which one molecule of gallic acid has the function of an alcohol, the other that of an acid. It is therefore transformed into gallic acid only by alkalies, acids, and ferments. Inversely, gallic acid, when boiled with ten per cent. of arsenic acid in watery solution, is entirely transformed into tannic acid—



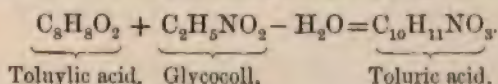
The arsenic acid undergoes no change in this process, and effects what used to be called a mere contact action. The formula formerly given by some chemists of tannic acid as a glucoside of gallic acid is not correct. The tannine so-called, which on chemolysis yields more or less sugar, is really tannic acid, mixed with varying quantities of a glucoside which may be that of digallic acid.

4. *Toluric Acid*, $C_{10}H_{11}NO_4$.

This acid was discovered and its formation synthetically explained by Kraut ("Ann. Chem." 98, 360). Toluylic acid, when taken in doses of several grammes, imparts to the urine which is voided afterwards a strongly acid reaction. It is evaporated to the consistence of a syrup, and extracted with alcohol. The extract is treated with oxalic acid, and again evaporated, and the residue extracted with ether containing some alcohol. This leaves on evaporation a yellowish, crystalline mass, mixed with oxalic acid. It is boiled with calcic carbonate when from the filtrate calcic tolurate crystallises. This, after repeated crystallisation, and decomposition with dilute warm hydrochloric acid,

yields, on the fluid cooling, crystallised *toluric acid* which, after recrystallisation from boiling water, is obtained pure in crystalline colourless plates. The solution in alcohol on spontaneous evaporation deposits large rhombic crystals. It forms salts with baryta, and oxyde of silver, and the alkalies, which are more soluble in hot than cold water. In cold, fuming, hydrochloric acid, toluric acid is soluble. If the solution, after short ebullition, is allowed to cool, toluric acid crystallises from it unchanged. But when this solution is boiled during several hours, the hydrochloric acid being replaced as it evaporates, and is lastly evaporated to dryness, a residue remains, which may be separated in two by treatment with water. This fluid leaves an amorphous substance undissolved, which may be recognised as toluylic acid, and transformed into the silver salt; the solution, after saturation with ammonia, evaporation, and addition of alcohol, leaves a precipitate, which is glykokoll. It may be identified by its property of dissolving oxyde of copper in watery solution, in which alcohol produces a precipitate of copper glykokoll.

Toluylic acid, therefore, like benzoic acid, combines with glykokoll in the animal economy, water being eliminated.



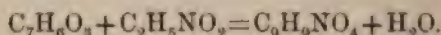
The third acid of the benzoic series, cuminic acid, does not exhibit this copulative property.

5. *Salicyluric Acid*, $\text{C}_9\text{H}_9\text{NO}_4$.

This acid was discovered by Bertagnini.

When about 6 grm. of salicylic acid in hourly doses of 0.25 grm. are taken internally there is no inconvenience attending the experiment on the first day; on the second day, however, noises in the ear and narcotic depression affect the experimentalist. Already an hour after the ingestion of the first dose, the urine gives a violet reaction on the addition of salts of iron, a peculiarity which continues during the entire duration of the experiment, and is yet present, though faintly, for forty-eight hours after the last ingestion of salicylic acid. The acid urine is evaporated down to a small bulk, and put aside for crystallisation of the salts. The decanted liquid is strongly acidified with hydrochloric acid, and repeatedly digested with ether. The ethereal solutions, on evaporation, leave a strongly acid fluid, which, on further evaporation, deposits crystals. These are purified by pressing between paper, recrystallisation, and treatment with animal charcoal. The substance so obtained is a mixture of small needles, and large, glistening, needle-shaped crystals; the former are salicylic, the latter salicyluric acid. It

dissolves in warm hydrochloric acid, and on cooling crystallises from the solution. By protracted boiling of this solution in hydrochloric acid, it is decomposed, and from the mixture, after neutralisation of the hydrochloric acid by means of calcic carbonate, ether extracts salicylic acid. In solution there remains glykokoll. This decomposition shows that the formation of salicylic acid in the body takes place according to the equation—



From its solution in hot water, salicylic acid crystallises in concentric groups of thin, glistening needles. It has a bitter taste and a strongly acid reaction. It is easily soluble in boiling, little soluble in cold water, easily soluble in alcohol, less in ether. These solutions impart a violet colour to salts of oxyde of iron, which colour disappears under the influence of concentrated acids. It fuses at 160° without loss of weight, and, on cooling, solidifies into an indistinctly crystalline mass. Towards 170° it begins to get brown, and is decomposed, salicylic acid being volatilised. If heated rapidly, it swells up, evolves ammonia, and leaves charcoal, which is combustible without leaving any residue.

When to a boiling solution of the acid in water calcic or barytic carbonate is added, an evolution of carbonic acid takes place, and the solution contains a salt of the acid with the respective metal. These salts are little soluble in cold water. There is also an insoluble calcium salt obtained by the addition of small portions of milk of lime to a hot solution of the acid, until the mixture solidifies to a mass of glistening scales.

6. *Salicylic Acid*, $C_7H_6O_3$.

It is a colourless oil, crystallising at 20° , and boiling at 196° . It has an agreeable odour and burning taste, is easily soluble in water, soluble in every proportion in alcohol and ether; it reddens litmus, and its watery solution gives with ferric chloride a violet, with caustic potash a yellow coloration. It reappears in the urine unchanged, and may be extracted from its concentrated residue by ether.

7. *Meconic Acid*, $C_7H_4O_7 + 3H_2O$.

It is one of the principal ingredients of opium. It crystallises in white scales, which lose their water of crystallisation at 100° . It is soluble in four parts of boiling water, much more soluble in alcohol. Very small quantities of meconic acid, or of its salts, yield a red coloration with ferric salts, which is not destroyed by feeble or dilute acids, but resolved by hypochlorites. The reaction which sulpho-cyanides give with ferric salts is very similar

to that of meconic acid, but is destroyed by gold chloride, which does not affect the reaction of meconic acid.

It has been asserted that meconic acid reappears in the urine after having been taken in opium. But the proof has not been furnished, and is now required all the more stringently, since we know that the red reaction of urine with ferric salts may be due to acetic, formic, and kryptophanic acid.

8. *Camphoric Acid*, $C_{10}H_{16}O_4$.

Experiments with this acid were made by Bertagnini ("Ann. Chem." 97, 248).

12 grm. of this acid in doses of about 0.5 grm. distributed over two days may be taken without inconvenience. The urine which is passed during that time is strongly acid, and contains unchanged camphoric acid. It is condensed to one-third of its original volume, and, after addition of hydrochloric acid, a crystalline deposit ensues. When the mother-liquor is shaken with ether, the latter, after evaporation, deposits another quantity of brown crystals. These are treated with milk of lime, whereby a soluble lime salt is obtained, which is decomposed by hydrochloric acid, whereupon a white crystallised substance is obtained, having all the properties and the composition of camphoric acid. It forms small rhombic prisms, without smell, of feebly acid taste, fusing at 62° 5, and again crystallising on cooling, subliming at a higher temperature, and yielding its anhydride and water.

9. *Anisic Acid*, $C_8H_8O_3$.

Experiments were made with this acid by Bertagnini.

When about 6 grm. of anisic acid are taken in the course of two days, a sensation of weight in the stomach is experienced. The urine has a strongly acid reaction, and after evaporation, addition of hydrochloric acid, and extraction with ether, anisic acid is obtained from the latter by evaporation.

According to Schultzen and Graebe, however, anisic acid combines in the body with glykokoll, and appears in the urine as anisuric acid.

Anisic acid crystallises from boiling water in needles, fuses at 175° , and sublimes between that temperature and 280° , at which latter it boils. In absence of characteristic reactions its identity has to be established by elementary analysis.

10. *Cuminic Acid*, $C_{10}H_{12}O_2$.

The bearing of this acid in the animal body was examined by Kletzinsky (Heller's "Archiv." 6, 95), Hofmann, and Kraut.

When this acid or any of its salts is taken internally it reappears unchanged in the urine, and can be extracted by the

process above described for camphoric acid. Cuminic acid forms white plates, which fuse at 113° , sublime in long needles, boil above 250° ; it floats as an oil on boiling water, is almost insoluble in cold, more soluble in hot water, easily soluble in alcohol and ether.

11. *Abietinic Acid.*

This acid, when taken into the stomach, is said to reappear in the urine. It is also stated that oil of turpentine and copaiba balsam, when taken internally, appear, at least in part, as abietinic acid in the urine.

12. *Various Acids.*

Benzoic acid, benzoic ether, oil of bitter almonds, cinnamic acid and chinic acid yield hippuric acid (*q.v.*). Mandelic acid is said to combine with glykokoll, and appear as mandeluric acid; nitrobenzoic becomes nitrohippuric acid. Citric and malic acid and their salts, when swallowed even in large doses, do not reappear in the urine.

CHAPTER LXVII.

UROPHANIC ORGANIC BASES AND INDIFFERENT BODIES.

INTRODUCTORY REMARKS.

Quinine and quinidine.	Cubebine.
Strychnine.	Santonine.
Morphine.	Salicine.
Veratrine.	Acetamide.

THE substances here to be considered may be innocuous matters, or medicines, or poisons. In respect of these two latter classes, the analysis of the urine becomes of peculiar importance as a key to the knowledge of the mode of action of medicines in the system, or as a guide to the discovery of the nature of a poison, under the influence of which an individual is labouring, or has died. Thus the analysis of the urine may lead to the prevention or discovery of crime. The merest medicinal dose of strychnia administered in any form makes its appearance in the urine. Thus, to the watchful medical practitioner, a source of information is afforded in cases where the ordinary symptomatology leaves him in uncertainty and doubt.

Quinine and Quinidine. $C_{20}H_{24}N_2O_2$

When quinine or quinidine, or both, are taken internally, a small portion escapes from the body by the kidneys in an unaltered state. To extract these alkaloids the following process of Herapath ("Quart. Journ. Microsc. Soc." Nr. 5, October 1853, p. 13) may be used:—

The urine is treated with caustic potash until decidedly alkaline; it is then repeatedly agitated with ether; the ethereal solutions are isolated and distilled from a flask. The residue contains a portion of the bases. Another portion remains in the magma of phosphates which floats below the ether, before decantation, above the urine; this is also removed, evaporated to dryness, and extracted with ether. The residue is added to

the first one. The united extracts are now tested for quinine as follows:—

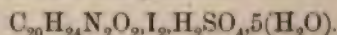
Test Fluid.

To a mixture of three drachms of pure acetic acid with one drachm of alcohol, six drops of diluted sulphuric acid (one acid to nine water) are added.

One drop of this test fluid is placed on a glass slide, and a minute particle of the alkaloid added; time given for resolution to take place; then, upon the tip of a very fine glass rod, a very minute drop of tincture of iodine added: if quinine be present, the first effect is the production of the yellow or cinnamon-brown coloured compound of iodine and quinine, which shows itself as a small circular spot, whilst the alcohol separates in little drops, which, by a sort of repulsive movement, drive the fluid away; after a time the acid liquid again flows over the spot, and the polarising crystals of sulphate of iodo-quinine are slowly produced in beautiful rosettes; this experiment succeeds best without the aid of heat.

To render these crystals evident, it merely remains to bring the glass slide upon the field of the microscope (having half-inch objective and lowest power eye-piece), with the selenite stage and single tourmaline beneath it: instantly the crystals assume the two complementary colours of the stage; red and green, supposing the pink stage is employed, or blue and yellow, provided that the blue selenite is made use of—all those crystals at right angles to the plane of the tourmaline producing that tint which an analysing plate of tourmaline would produce when at right angles to the polarising plate; whilst those at 90° to these educe the complementary tint, in the same manner as the analysing plate would have done if it had been revolved through an arch of 90° .

These crystals are then proved to be the sulphate of iodo-quinine, and to have the composition—



To test for quinidine it is merely necessary to allow the drop of acid solution to evaporate spontaneously to dryness upon the glass slide (before and without the addition of iodine), and to examine the crystalline mass by two tourmalines crossed at right angles, and without the selenite stage; immediately little circular disks of white, with a well-defined black cross very vividly shown, start into existence, should quinidine be present even in minute quantities. When large doses of quinine and quinidine sulphate, up to 3 grm. in 24 hours, are taken, about one quarter reappears in the urine. The other three quarters are assimilated or destroyed by the body during their transit.

Quinine can also be shown to be present in urine by means of its blue fluorescent action on electrical light. As the presence of chlorine prevents the action, it has to be removed by mercurous nitrate added to the urine. But the very delicacy of the test, and the possible presence of the animal quinoidine of Dupré and Bence Jones, make fluorescence experiments on urine of little or no practical value.

Strychnine, $C_{21}H_{22}N_2O_2$.

Strychnine, when introduced into the animal economy in any notable quantity, per example, in the ordinary medical doses at from one-tenth to one-twentieth of a grain, repeated at intervals, reappears in the urine.

The diagnostic properties of strychnine are, its bitter taste, even in extremely dilute solutions, and the violet and blue, or purple reaction, under the influence of bichromate of potash, and sulphuric acid. It is little soluble in water, alcohol, or ether, more soluble in boiling alcohol, and crystallises from this solution on cooling. Its acid salts, however, are easily soluble in water and alcohol, and may by means of these agents be extracted from organic substances. The residue of this extraction by water and alcohol, containing the acid salts, having been made alkaline by caustic potash, yields all its strychnine to chloroform, which, after evaporation, leaves it more or less pure.

Mode of Extracting Strychnine from Urine.

In order to obtain strychnine from urine, it is necessary to evaporate this fluid to the consistence of a thin syrup, to make it strongly alkaline by caustic potash, and to shake it with large and repeated quantities of chloroform. The chloroform solution is distilled, and the residue treated with concentrated sulphuric acid on the water-bath. After several hours' digestion the acid is neutralised by carbonate of sodium, the fluid is then made alkaline, and again extracted with chloroform, which after evaporation will leave strychnine, to be tested by the taste, and by the reaction with bichromate of potash and sulphuric acid. This latter reaction is best effected in the following manner:—The solution in water of the supposed alkaloid is placed in a small porcelain dish, and after evaporation to dryness, at a low temperature, is dissolved in a drop or several drops of sulphuric acid. This solution is now spread over the space of about a fourpenny piece. A small granule of bichromate of potassium is now dropped into the solution. On moving the fluid, by giving the porcelain dish different inclinations, violet streaks are perceived to flow from the granule of bichromate, and on moving the crystal to and fro in the fluid, by means of a glass rod, the entire solution soon assumes a fine purple colour.

One grain of a solution of strychnine, containing one forty-thousandth part of a grain of solid strychnine, yielded this test quite clearly. Five drops of the same solution brought upon the tongue had a decidedly bitter taste; on some occasions two or three drops would permit the bitterness to be recognised.

Morphine, $C_{17}H_{19}NO_3$.

According to Dragendorff ("Pharm. Zeitschr. Russland," 1868, Heft 4, and "Ermittl. von Giften," 1868, p. 295), Bouchardat, and Lefort, morphia passes into the urine in considerable quantity. It can be extracted by shaking the alkaline liquid with much amyl alcohol. The residue from this solution may be tested as follows:—A test fluid is made containing in every c.c. a milligram. of sodic molybdate (Fröhde, "Arch. f. Pharm." 176, 54). This, in contact with any morphia, immediately dissolves it with a violet colour; the mixture then becomes green, brownish-green, yellow; after 24 hours it is violet-blue. Further, a small quantity of the residue supposed to contain morphine, is dissolved in concentrated sulphuric acid, and after standing during from 15 to 18 hours (!) is mixed with a small trace of concentrated nitric acid. If morphia is present, the mixture becomes violet-blue, blood-red, and then deep orange. Instead of letting the solution stand, it may be heated to 150° , and cooled again to 15° before applying nitric acid (Husemann).

Veratrine, $C_{32}H_{52}N_2O_8$.

Veratrine passes quickly into the urine of poisoned animals. Veratrine passes from an acid watery solution into warm amyl alcohol, if both liquids are well agitated with each other. From an alkaline liquid veratrine passes at 50° to 60° into petroleum ether and into chloroform. With pure sulphuric acid veratrine gives a solution which passes from yellow to orange, and becomes carmine within half an hour. Heated for some time with concentrated hydrochloric acid, a trace of veratrine assumes a beautiful red colour.

Of *Theine*, *Caffeine*, *Theobromine*, or *Aniline*, it is not known whether or not, in the original or an altered form, they appear in the urine.

Cubebine is excreted by the urine (Bernatzik).

Santonine, $C_{15}H_{18}O_3$.

When santonine is administered internally, the normal urine does not appear to have undergone any change when afterwards passed. If the urine be, however, by any accident alkaline, it has a fine red colour. In the acid and unchanged urine passed after the ingestion of santonine, this red colour may be produced by ammonia, and the fixed alkalies and earths, also by the car-

bonates, tribasic phosphates, and borates of the alkalies. The phosphates, which are thereby precipitated, are coloured red by adhering pigment. If this alkaline red urine is left to stand, it sooner or later becomes yellow again, and the red colour cannot again be produced by either acids or alkalies. The red colour of urine, produced in common acid yellow urine passed after ingestion of santonine, may be made to disappear quickly by shaking with oxygen gas, or by passing ozone through it, which latter is perfectly absorbed during its passage. Santonine may be swallowed in doses increased gradually from one half to three grains. Fifteen grains have besides a slight diuretic, no other effect. Twenty hours after ingestion, the last traces of the urinary pigment produced by the santonine can be perceived in the urine.

CHAPTER LXVIII.

UROPHANIC SPECIFIC METAMORPHIC PRODUCTS.

- (1.) *Products of Asparagus, Asparagine, Asparaginic Acid.*
- (2.) *Products of the Metamorphosis of Chloral.*

INFLUENCE OF ASPARAGUS UPON THE URINE.

HILGER ("Ann. Chem." 171 (1874), 208) has made some observations on this subject. He ate during three days, as only food, asparagus with oil and vinegar and a little bread, and drank beer. The total urine collected amounted to 5100 c.c. Of this 3000 c.c. were subjected to distillation, but although the distillate had the peculiar odour in a high degree, no definite body owning the odour could be isolated, and what was obtained was ammonia amounting to 6.24 gm. Another 500 c.c., treated with soda lime in the cold, gave to sulphuric acid of known strength 1.02 gm. ammonia. From this Hilger ventured to conclude that the ammonia was increased beyond the normal by decomposition of asparagine in the organism.

The urine, and the residues from the distillation contained no asparagine, but there were formed relatively large quantities of succinic, an increased quantity of hippuric, and some benzoic acid. The succinic acid, as well as the ammonia, Hilger explains as the result of a splitting up of asparagine. But the augmentation of the other acids he does not attempt to explain.

Knieriem ("Zeitschr. f. Biol." 10 (1874), 263), however, in a series of most accurate researches, found that asparaginic acid, and asparagine, when introduced into the body of a dog, were transformed into urea. A dog of 7 kilos weight bore doses of asparagine up to 19 gm. without being inconvenienced thereby. The amount of urea excreted afterwards was nearly treble the one excreted after ordinary diet.

Products of the Metamorphosis of Chloral.

According to O. Liebreich chloral hydrate is decomposed in the blood, forming chloroform and formic acid. But it has repeatedly been attempted without success to extract these bodies from the blood or the expired air. Külz and Bouchut stated that they

had found chloroform in urine; Hammarsten failed, however, in discovering it. Tomasevics could find chloral, but no chloroform. Mering and Musculus ("Ber. Deutsch. Chem. Ges." 8, 662) examined the urine of individuals who had taken for some time every evening 5 to 6 grm. of chloral hydrate. The urine was acid and reduced copper solution, but this reaction was not caused by sugar; chloroform and formic acid were also absent, but the presence of small quantities of chloral could be proved by the reaction of isocyan phenyl. The urine turned the polarised ray to the left.

Mode of Isolating the Metamorphic Product.

The urine is evaporated to a syrup, mixed with sulphuric or hydrochloric acid, and exhausted with ether containing some alcohol. The ether is removed by distillation, the residue neutralised with potash, evaporated, taken up with alcohol of 90 per cent. filtered, precipitated with ether, the precipitate is dissolved in water, decolorised with animal charcoal, and concentrated. The potash salt which is deposited on cooling is dried over sulphuric acid, and washed with absolute alcohol until it is white. To isolate the acid the salt is dissolved in little water, mixed with hydrochloric acid, shaken with a mixture of 2 vols. ether with 1 vol. alcohol, and filtered. To the filtrate much ether is added; the mixture is allowed to stand during 48 hours, decanted, and the ether is distilled off. To the residue moist silver oxyde is added, to remove chlorine. The filtrate is treated with hydrothion to remove silver, and the solution evaporated to crystallisation.

The new acid has the formula $C_7H_{12}Cl_2O_6$. This has not been controlled by atomic weight determination. It crystallises in colourless silky needles, resembling tyrosine, is soluble in water, alcohol, alcohol-ether, not in pure ether, reddens litmus and decomposes carbonates. It reduces copper strongly, and turns the polarised ray to the left. Some salts crystallise. It is possible that the acid is formed by the combination of chloral, or of some part of it, with some principle of the body at present unknown.

CHAPTER LXIX.

UROPHANTIC INORGANIC SUBSTANCES.

INTRODUCTION.

Arsenic and Antimony.	
Lead.	
Mercury.	
Copper.	
Iodine.	
Bromine.	
Ammonia.	
Carbonates	} of alkalies.
Silicates	
Chlorides	
Borates	
Sulphocyanide or rhodanide	} of potassium.
Ferricyanide	
Ferricyanide changed into ferrocyanide	
Rhodalline, as ammoniac sulphocyanide.	
Chlorate	} of potassium.
Nitrate	
Sulphuret of potassium.	
Chloride of baryum.	

ARSENIC AND ANTIMONY.

IN cases where these metals, or either of them, should be present in urine in any considerable quantity, they would be precipitated as sulphides by a current of hydrothion conducted through the acidified liquid. But mostly their quantities are very small, not so much because these poisons are sparingly eliminated by the kidneys, as because (in cases of poisoning) the urine containing the largest proportion is mostly not to be obtained.

When these substances have been taken by or administered to any person, either in medicinal doses, or by accident or criminal design, the urine of the patient voided some time afterwards almost always contains some arsenic or antimony, so that Orfila was induced to recommend a diuretic treatment in cases of poisoning by either of these substances.

Method of Obtaining Arsenic and Antimony from Urine by Copper.

The urine is evaporated to a small bulk, and then from one-sixth to one-seventh of its volume of pure hydrochloric acid is

added to it. It is boiled; and while boiling, a small piece of thin copper foil or gauze, known and specially ascertained to be free from arsenic, freshly brightened by rubbing with some oxalic or hydrochloric acid and paper, is introduced. Sooner or later, according to the quantity present, antimony, or arsenic, or both, are deposited on the copper, producing a blackish-grey, or grey deposit, with a reddish-violet or purple tint if antimony in small quantities is deposited: but an iron grey or black tint if antimony in large quantities, or arsenic, are deposited. If no deposit is observed at first, the whole of the liquid must be boiled down on the copper, before the inference is drawn that arsenic or antimony are absent. If the copper be removed without any metallic tarnish or deposit upon its surface, there is no antimony or arsenic present. If it has acquired a metallic deposit, then, after well washing, and drying it, the following steps must be resorted to in order to determine the nature of the metallic coating.

Diagnosis of Arsenic and Antimony.

The copper foil is placed in a tube, which is closed at one end, and heated. A grey or dark metallic ring deposited at the cold part of the glass tube consists of arsenic. A white sublimate deposited beyond the black ring, and seen under the microscope to consist of cubes and octahedra, is arsenious acid.

Antimony is not sublimed under these circumstances.

The copper foil is placed into a concentrated alkaline solution of hypochlorite of soda; the metallic deposit of arsenic is immediately or slowly dissolved. The presence of small quantities of antimony does not interfere with this reaction, any further than that the antimony remains undissolved.

If the copper foil, after having undergone the above tests, still retains a metallic coating, it is boiled in a weak solution of potash, the metal being partly exposed to air by drawing it out of the alkaline liquid, and then again returning it. In this way the antimony is oxydised by the air in contact with an alkaline solution, and antimoniate of potash is formed. In about five or ten minutes the copper will have lost the deposit, and the liquid may then be filtered, acidulated with hydrochloric acid, and treated with sulphuretted hydrogen. The sulphide of antimony, of its characteristic orange-red colour, is thrown down, either immediately, or on allowing the liquid to stand for a short time.

LEAD.

Method of Obtaining Lead from Urine.

It is necessary to employ not less than one day's urine for this operation, which is the more likely to be successful the larger the quantity of urine employed.

The urine, after being made alkaline by caustic potash, is mixed with two per cent. of its weight of nitrate of potassium, and evaporated to dryness. The residue is now transferred into a small porcelain capsule, and exposed to red heat, when a slow deflagration destroys the whole amount of organic matter present. On cooling there remains a white slaky mass, not adhering to the capsule, and containing all the inorganic fixed ingredients of the urine, together with the lead that may have been present. This slake is powdered finely, and boiled for some time with a half-saturated solution of neutral tartrate of ammonium, to which some caustic ammonia has been added. The decoction is freed from the residue by filtration; the filtrate contains all the lead in solution. It is acidulated by means of hydrochloric acid, and a current of sulphuretted hydrogen is allowed to pass through it. A brown discoloration, or a black precipitate, indicates the presence of a poisonous metal, which from the history of the case may be supposed to be lead. The precipitate is allowed to deposit for twenty-four hours, washed by decantation, redissolved in warm *dilute* nitric acid, and the filtrate from the precipitate of sulphur, after neutralisation, is tested by means of chromate of potassium and sulphuric acid. The chromate yielding a yellow, the sulphuric acid a white precipitate, excludes any doubt as to the black precipitate having been sulphuret of lead.

In only two out of fourteen cases of distinct lead poisoning examined in this manner, the presence in the urine of lead can be proved by the latter tests. In the twelve remaining, the presence of lead is only indicated by the brownish colour produced in the acid solution by hydrothion.

MERCURY.

The urine should be evaporated to dryness, and the organic residue destroyed with nitric acid. The ash which then remains is mixed with sodic carbonate, containing a little potassic dichromate, filled into a combustion tube, and after the latter has been drawn out to a thin tube at the open end, ignited. The mercury is expelled and collects as a film or in globules in the first part of the drawn out tube; the latter must be kept very cool during the operation. The mercury can be estimated by cutting out the part containing it, and weighing glass and mercury. The mercury may then be removed by heating the piece of tube, and weighing it again, when the loss will be equal to the quantity of mercury volatilised. Or the mercury may be dissolved by nitric acid, and the piece of tube weighed as before. The nitric acid solution then affords the opportunity of identifying the sublimate as mercury.

COPPER.

The urine is treated on the water-bath with chlorate of potas-

sium and fuming hydrochloric acid, until the organic matters and the chlorate are entirely destroyed. The pale yellowish solution is now made alkaline by an excess of ammonia, whereby its colour changes into brown, with a smoky hue. Any precipitate that may ensue is removed by filtration. The filtrate is evaporated on the water-bath to perfect dryness, the residue moistened with nitric acid of 1.5 sp. gr. and exposed to red heat in a porcelain capsule. The ashes, which must not contain any charcoal, are dissolved in hydrochloric acid, and this solution is boiled under addition of little nitric acid, in order to ensure the highest possible oxydation of the metals, iron and copper, of which the former is always present in urine. This acid solution is now treated with excess of ammonia, whereupon a precipitate of hydrated oxyde of iron falls down, which must be removed by filtration. If the filtrate has a bluish colour, and after being acidulated with acetic acid, yields a reddish turbidity or reddish-brown precipitate with ferrocyanide of potassium, the presence of copper is proved. This proof may be further strengthened by acidulating the alkaline solution by hydrochloric acid, and conducting a current of sulphuretted hydrogen through it; a brownish turbidity, soluble in sulphuretted ammonium, with a brown colour, is indicative of copper. Another test consists in putting a piece of blank iron foil, surrounded by a spiral wire of platinum, into the solution, acidulated by hydrochloric acid. After several hours the iron is covered by a red hue if copper is present in the solution.

In most cases of poisoning by copper compounds this metal can be found in the urine as long as any symptoms remain about the patients. When the symptoms cease the copper disappears from the urine, but continues to be discharged with the *faeces*. The *faeces* of healthy persons mostly contain some copper; healthy urine, however, does not contain any traces of this metal.

IODINE.

Iodine is frequently used as a medicine, and its effects are sometimes irregular, though it has been given with a due regard to experience. It is necessary to ascertain the reasons of this variable action; and for this purpose the analysis of the urine will best serve. For one of the principal reasons why iodine and its preparations are borne very well by some, and have injurious effects in others, is the varying length of time required for its removal from the body. It has been found that when several persons each take a dose of 10 grains of iodide of potassium, some will immediately begin to excrete it in their urine, which after the lapse of twenty-four hours no longer contains any trace of the iodide. In others, however, the iodide can frequently be found even after the lapse of three days. Supposing the daily

dose of 10 grains to have been administered for a length of time to these two classes of people, the first class would most probably never have at one time more than 10 grains of the iodide in their body, while the latter might have 30 or 40 grains in their body at one time. Not only, therefore, would the action of the drug in these latter cases go parallel to the quantity present, but also it would last much longer; and in this way equal doses at equal intervals might in the latter class produce four times the effect they would produce in the first class. In some cases, therefore, where an explanation of an extraordinary mode of action of iodine or iodides may be necessary or desirable, the analysis of the urine will be the chief source of information on this point, due consideration being given to other excretions, by which iodine is removed from the economy.

Mode of Estimating the Quantity of Iodine in Urine by Weight.

A measured quantity of urine is strongly acidified by nitric acid, and the chlorine and iodine are completely precipitated by silver nitrate. The precipitate is washed, dried, and weighed in a Liebig's drying apparatus. Chlorine is then passed through the tube over the precipitate, until the weight of the tube is constant when filled with air. All the iodine is then driven out and substituted by chlorine. From the difference in the weights the amount of iodine originally present is easily calculated.

Volumetrical Analysis of Iodine in the Urine.

A very dilute solution of iodine or an iodide yields all the iodine by distillation with sulphuric acid. In the distillate, the amount of iodine is determined by a solution of subchloride of palladium of known strength. In the performance of this analysis care must be taken never to have an *excess* of the solution of iodine mixed with the solution of palladium, as in that case the fluid does not get clear very quickly, and the precipitate of iodide of palladium adheres to the walls of the glass. But when the solution of palladium is present in slight excess together with a little hydrochloric acid, and the mixture is warmed to from 60° to 100° , and agitated, the iodide of palladium, after a few seconds, separates in black flakes, and the supernatant fluid is perfectly clear and colourless. In performing the analysis, therefore, to a known volume of the solution of palladium of known strength, such a volume of the solution of iodine to be analysed is added, as is just sufficient to precipitate the entire amount of palladium in solution. This analysis is so accurate that $\frac{3}{100}$ th milligram. of iodine may be determined by means of the palladium, and $\frac{1}{1000}$ th milligram. of palladium by means of iodine.

Preparation of Solution of Iodide of Potassium of known Strength.

This solution is to be so graduated that every part of it contains $\frac{1}{1000}$ th part of iodine. For that purpose 1.307 grm. of dry iodide of potassium, perfectly free from iodate of potassium, are dissolved in water, and the solution is diluted until amounting to one litre. 1 c.c. of this solution contains 1 milligram. of iodine, as 1.307 grm. of iodide of potassium contain 1 grm. of iodine.

Solution of Subchloride of Palladium of known Strength.

We prepare a solution of palladium of unknown strength, and graduate it by means of the solution of iodide of potassium just described. 1 grm. of the metal is dissolved in aqua regia, with the aid of heat, and evaporated to dryness on the water-bath. After solution of the residue in 50 c.c. of concentrated hydrochloric acid, water is added to the amount of about 2000 c.c. The exact amount of palladium contained in a given volume is now determined by means of the solution of iodide of potassium of known strength, in the following manner:—10 c.c. of the solution of palladium to be graduated are put into a flask of about 200 c.c. capacity. The flask is closed by a cork stopper, and warmed in a water-bath to near boiling heat. From a burette the graduated solution of iodide of potassium is now added, the mixture shaken, and warmed again. Four minutes will suffice to separate the mixture into a precipitate, which subsides towards the bottom of the vessel, and a clear supernatant fluid. Of the latter two portions are each put in a test-tube. To the one portion a few drops of the solution of iodide of potassium are added; and, by comparison with the other test-tube, we find whether a brownish tint has been produced by the iodide. In case a brownish precipitate has been produced, the two portions are again poured back to the main bulk of fluid, to which some more solution of the iodide is added under agitation, and warming, and so on, until in a fresh portion of the clear supernatant fluid no discoloration is produced by the addition of the iodide test fluid. At this stage of the proceeding the fluid is separated from the precipitate by filtration; and if a sample of it is not tinted brown by either solution of palladium or iodine, the fluid does not contain a trace of excess of either substance, and the analysis is completed. From the equivalent of the iodine used the amount of palladium contained in the 10 c.c. used for analysis may be found by calculation. 1 milligram. of iodine is equivalent to 0.42 milligram. of palladium, which is therefore the quantity indicated by every cubic centimetre of the graduated solution of iodide of potassium.

Supposing the 10 c.c. of solution of chloride of palladium required for the complete precipitation of palladium contained in

it, 11.9 c.c. of graduated solution of iodide of potassium, containing 11.9 milligram. of iodine, then the amount of palladium contained in the 10 c.c. of solution was 11.6×0.42 milligram. = 4.998 milligram. The same volume of solution of palladium would therefore require such an amount of solution of iodine of *unknown* strength as would exactly contain 11.9 milligram. of iodine. From the amount thus used the amount of iodine contained in the entire bulk of fluid is ascertained by calculation.

Application to the Urine.

100 c.c. or more of urine are mixed with 20 c.c. of concentrated sulphuric acid, and kept in a cold water-bath during the first violent evolution of heat. The flask containing the mixture is then connected with a Liebig's cooler, and the distillation proceeded with. It is continued until, in the neck of the flask, white vapours of sulphuric acid begin to appear. If, however, the urine contains only a very small amount of iodine, any measured quantity, after addition of an excess of caustic potash, may be concentrated by simple evaporation of the water, and only then distilled with sulphuric acid in the manner described.

The distillate thus obtained contains hydriodic acid, all volatile acids of the urine, with carbonic, sulphurous, and sulphuric acids. The sulphurous acid must be oxydised before the fluid can be subjected to further analysis. This is effected in the following manner:—To the distillate are added a few drops of solution of starch (made of 1 part of starch, $\frac{1}{8}$ th part of sulphuric acid, and 24 parts of water), and after that a saturated solution of chloride of lime in drops, until the fluid just begins to get blue. The blue colour is then again made to disappear by one or two drops of a dilute solution of sulphurous acid in water. The volume of the entire solution is now measured, and the necessary quantity of it filled into a Mohr's burette, and from this added to the 10 c.c. of solution of chloride of palladium in the manner above described, until the entire amount of palladium is precipitated.

Thus, if 100 c.c. of urine yielded 96 c.c. of distillate, and if of this distillate 12 c.c. were required for precipitating the 4.998 milligram. of palladium from the 10 c.c. of solution, then the 12 c.c. contain 11.9 milligram. of iodine. The 96 c.c. of distillate, therefore, corresponding to 100 c.c. of urine, contain $8 \times 11.9 = 95.2$ milligram. of iodine.

According to Hilger ("Ann. Chem." 171 (1874), 217), it is not advisable to distil the urine with sulphuric acid to obtain hydriodic acid, but it is less troublesome and safer to apply the palladium subchloride to the urine direct, without any other preparation than acidification of the urine by hydrochloric acid.

A solution of subchloride of palladium of known strength

is first produced by titration with solution of potassic iodide of known strength. The urine is then tested qualitatively for iodine, and the reaction obtained used for guessing at the probable amount. According to this test, 10 to 20 c.c. of solution of palladium subchloride are placed into a flask provided with a ground glass stopper, and heated. The urine, acidified with hydrochloric acid, is now added to the palladium solution from a graduated burette until all palladium is precipitated, as iodide. The mixture must be strongly shaken from time to time in order to cause the precipitate to unite and settle. The point at which enough urine has been added to the palladium solution must be ascertained by filtering a small sample of the mixture, and testing it with either some urine or some palladium solution; if neither gives a turbidity the test is completed. From the strength of the palladium solution, as ascertained by potassic iodide, the amount of iodine contained in the quantity of urine used is easily calculated.

Of other inorganic substances introduced into the system the following have been found to make their appearance in the urine :—

Bromine and bromides.

Ammonia and its salts.

Carbonates	} of alkalies.
Silicates	
Chlorides	
Borates	

Sulphocyanide, or rhodanide

Ferrocyanide

Ferricyanide changed into ferrocyanide	} of potassium.
Rhodalline, as sulphocyanide of ammonium.	

Chlorate

Nitrate	} of potassium.

Sulphuret of potassium reappears partly as such, partly as sulphate of potassium.

Chloride of baryum.

CHAPTER LXX.

SCHEME OF SYSTEMATIC QUALITATIVE ANALYSIS OF URINE AND URINARY SEDIMENTS.

TEST the action of the urine with litmus.

1. It is acid and has no sediment, proceed to 2.

II It is acid and has a sediment; pour off the clear liquid, filtering if necessary, and proceed to analyse the filtrate according to 2. Examine the sediment dry.

1. Heat a sample of urine to boiling after the addition of some acetic acid. A coagulum forms, which does not disappear on the addition of nitric acid: *albumen*.

Boil some quantity (500 c.c.) of the urine with acetic acid; filter off the coagulated albumen and treat the filtrate as under 2.

a. The coagulum is white, *pure albumen*.

b. The coagulum is greenish; albumen, probably coloured by bile.

c. The coagulum is brownish-red: probably from blood; wash and dry the coagulum; boil with alcohol containing a little sulphuric acid; if the filtrate is reddish examine with spectroscope for acid hematine or evaporate to dryness, ignite, moisten the ash with a drop or two of concentrated hydrochloric acid, dilute with a little water, filter the solution through a small filter, and add to the filtrate a little potassium sulphocyanide; a red colour confirms the presence of blood.

2. Take 400 to 500 c.c. of the clear urine filtered from coagulated albumen or sediment; evaporate in a porcelain dish on a water-bath to a thick syrup; divide the syrup into two parts, one equal to one-third the other two-thirds of the whole.

Extract the third with strong alcohol; filter, and examine the filtrate.

1. Evaporate a small portion nearly to dryness, and add a little nitric or oxalic acid, and observe the crystalline forms of *urea nitrate* or *oxalate*.
2. Precipitate the larger portion with a few drops of milk of lime and calcium chloride solution and filter; concentrate the filtrate on the water-bath to 10–12 c.c. Transfer to a beaker, add one-half c.c. of strong alcoholic solution of zinc chloride, stir well and allow to stand; *kreatinine chloride of zinc* crystallises out in warty grains.
- b. Acidify the two-thirds with hydrochloric acid, and extract with ether. Evaporate the ethereal solution, and examine the residue for *hippuric acid*.
 1. The filtrate will contain *earthy phosphate* and other salts; add ammonia; the *earthy phosphates* will be precipitated.
 2. The insoluble residue consists of *mucus* and *uric acid*. Wash off the filter into a test tube, add one or two drops of caustic soda, warm and filter. The insoluble residue is *mucus*. The filtrate contains uric acid and hydrochloric acid; the *uric acid* separates out in crystals; collect and examine under the microscope, also verify by applying the murexide test, the presence of *uric acid*.
 3. The urine is brown or green; froths on shaking; colours a small piece of immersed filter-paper yellow or green; probable presence of *bile matter*.

Place some of the urine upon a white plate, and drop in a little strong nitric acid containing some nitrous, without shaking. The fluid turns successively green, blue, violet, and brown; presence of a derivate of colouring matter of the bile.

To a second portion add some lead acetate in solution; collect the precipitate, wash, dry, and boil the dried precipitate with alcohol, to which a little sulphuric acid has been added, filter; the filtrate is green from *biliprasine*.

Evaporate a third portion of 3 to 500 c.c. on the water-bath, extract with alcohol; search for biliary acids, tauro- and glykocholic.
 4. Take 1 c.c. of urine, dilute it with 4 to 5 c.c. of water, add $\frac{1}{2}$ a c.c. of caustic soda, and one drop of a very dilute solution of copper sulphate; boil; a red granular precipitate of suboxyde of copper indicates the presence of *sugar*.

5. Immerse in the urine a piece of filter-paper moistened with acetate of lead solution, if the lead paper turns brown or black *sulphuretted hydrogen* is present.

6. Evaporate 40 to 50 c.c. of the urine to dryness, ignite the residue at a moderate heat till all the charcoal has been burnt off; boil the residue with water and filter.

a.—1. Acidify a portion of the filtrate with hydrochloric acid; add baryum chloride; a white precipitate proves the presence of *sulphuric acid*.

2. Acidify a second portion with nitric acid, add a drop of silver nitrate; a white curdy precipitate indicates *hydrochloric acid*.

3. Acidify a third portion with acetic acid, add a little ferric chloride solution, a yellowish-white, gelatinous precipitate indicates *phosphoric acid*.

4. Evaporate the rest to dryness; take up a small portion on the end of a platinum wire and expose in a Bunsen or spirit lamp flame; a vivid yellow colour proves the presence of *sodium*.

5. Dissolve a portion in a little water, add a drop or two of solution of platinic chloride; a yellow crystalline precipitate indicates *potassium*.

b. Boil the residue insoluble in water with a little dilute hydrochloric acid, filter.

1. Boil a portion with a drop of nitric acid, add some potassium sulphocyanide solution; a deep red colour proves presence of *iron*.

2. Mix the rest with an excess of sodium acetate, add an excess of ammonium oxalate; a white precipitate proves the presence of *calcium*.

3. Filter off the lime precipitate, add to the filtrate ammonia; a white crystalline precipitate indicates the presence of *phosphate of magnesia*.

7. Add to 50 or 100 c.c. of the fresh urine contained in a flask, a little milk of lime, mix and cork loosely, suspending a moistened red litmus paper between the cork and the side of the flask. If the paper turns blue the presence of *ammonia* is proved.

8. Distil some urine with sulphuric acid, add to the distillate a little red fuming nitric acid, and then shake up with a drop of carbon disulphide, which, if *iodine* be present, will be coloured pink.

For acetic, benzoic, and kryptophanic acid, and for urochrome and its products, see separate articles.

Examination of the Sediment.—Allow any sediment to deposit at the bottom of a cylindrical glass. Pour off as much of the liquid as possible, then take up a little sediment with a pipette, place on a glass slide, and examine with the microscope.

A. The urine is acid.

I. The whole of the sediment seems amorphous.

1. On gently warming the whole dissolves : *urates* ; confirm by adding a drop of hydrochloric acid ; leave half an hour, when, if uric acid be present, it will have crystallised out in rhombic tables.

Also confirm by the murexide test.

2. The sediment does not dissolve on warming, but dissolves in a drop of acetic acid without effervescence ; presence of *calcium phosphate*.
3. Glistening drops appear in the sediment and disappear on the addition of ether : *fat globules*.

II. The sediment contains well-formed crystals.

1. Small, glistening, transparent octohedra, insoluble in acetic acid : *calcium oxalate*.
2. 4-sided tables or 6-sided rhombic plates often appearing grouped in bunches of spindle-shaped crystals : *uric acid* ; confirm by the murexide test.
3. Regular 6-sided tables soluble in hydrochloric acid and ammonia, which char on heating. Boil with caustic soda containing a drop of very dilute acetate of lead ; a black precipitate of sulphide of lead confirms the presence of *cystine*.
4. Wedge-shaped prismatic crystals, some separate, some united, to form a cross : *calcium phosphate*.
5. Greenish-brown grains with a radiating crystalline structure : *tyrosine*.
6. Needles or rhombic prisms easily soluble on warming : *hippuric acid*.

III. The sediment contains organised bodies.

1. Twisted fringy bundles, forming points, grains, &c. : *mucus*.
2. Contracted granular bodies, often united into a scale pavement-like mass : *mucus corpuscles*.
3. Circular biconcave disks, mostly yellowish, which swell up and more or less completely dissolve in acetic acid : *blood corpuscles* ; confirm by spectroscopic reactions.

4. Round, pale, faintly-granular vesicles, of different sizes, which swell up considerably in acetic acid, lose their outward granular surface, and allow an inner nucleus of different form to be seen: *pua*.
5. Cylindrical masses with small vesicles, often mixed with blood and pus corpuscles: so-called *casts of the tubules*.
 - a. Casts whose roundish nuclei are clearly visible through a delicate surrounding mass: *epithelial casts of Bellini's tubes*, mostly accompanied by the nucleated, epithelial cells of ureters and kidneys.
 - b. Solid cylinders of thick, granular, nucleated nature are *granular renal casts*, and often contain blood and pus corpuscles with fat globules, crystals of calcium oxalate.
 - c. Pale, transparent, solid cylinders, only seen with great difficulty: *hyaline casts*.
6. Epithelial cells.
 - a. Pavement epithelium.
 - b. Epithelial tubes.
7. Fermentation and thread fibres.
8. Short fine rods, threads, or square lumps, moving about in an undulating manner: *Vibrios*, *Spermatozoa*, *Sarcina ventriculi*.

B. The urine is alkaline.

I. Crystalline sediment.

1. Rhombic vertical prisms soluble in acetic acid; on mixing with a little milk of lime ammonia is evolved: *ammonio-magnesian phosphate*.
2. Wedge-shaped opaque masses giving the murexide reaction: *ammonia urate*.

II. Sediment is amorphous, usually *calcium phosphate*.

III. Sediment contains organised bodies, see above under A III.

CHAPTER LXXI.

SCHEME OF SYSTEMATIC QUALITATIVE ANALYSIS OF URINARY CALCULI.

POWDER the calculus. Heat a small portion of the powder to redness on some platinum foil, and observe whether any residue is left which will not burn off.

A. In case it leaves a fixed residue, take a small portion of the original calculus, dissolve in concentrated nitric acid, evaporate to dryness on a water-bath in a white porcelain evaporating dish; dip a glass rod into the strongest ammonia, and bring it near the residue in the dish, and observe whether a pink colour is produced or not.

I. A pink colour is produced, proving that the calculus contains *uric acid*; observe whether a portion of the calculus melts on being heated.

a. It melts—

1. And communicates a strong yellow colour to the flame of a spirit lamp or Bunsen burner: *sodium urate*.
2. And communicates a violet colour to the flame, giving the potassium spectrum: *potassium urate*.

b. It does not melt; dissolve the residue left after ignition in a little dilute hydrochloric acid, add ammonia till alkaline, and then ammonium carbonate solution.

1. A white precipitate falls: *calcium urate*.
2. No precipitate; add some hydric sodic phosphate solution; a white crystalline precipitate falls: *magnesium urate*.

II. No pink colour is produced. Observe whether a portion of the calculus melts on being heated strongly.

a. It melts (fusible calculus). Treat the residue with acetic acid: it dissolves; add to the solution ammonia in excess; a white crystalline precipitate falls: *ammonio-magnes-*

ium phosphate. In case the melted residue is insoluble in acetic acid, treat with hydrochloric acid; it dissolves. Add to the solution ammonia; a white precipitate indicates *calcium phosphate*.

- b. It does not melt; moisten the residue with water, and test its reaction with litmus paper; it is not alkaline. Treat with hydrochloric acid, it dissolves without effervescence. Add to the solution ammonia in excess, white precipitate: *calcium phosphate*. Treat the calculus with acetic acid; it does not dissolve. Treat the residue after heating with acetic acid, it dissolves with effervescence: *calcium oxalate*. Treat the original calculus with acetic acid, it dissolves with effervescence: *calcium carbonate*.

B. The calculus on being heated does not leave a fixed residue. Treat a portion of the calculus with nitric acid, evaporate and expose to ammonia vapour as before.

I. A pink colour is developed.

- a. Mix a portion of the powdered calculus with a little lime, and moisten with a little water; ammonia is evolved and a red litmus paper suspended over the mass is turned blue: *ammonium urate*.

b. No ammonia: *uric acid*.

II. No pink colour is developed.

- a. But the nitric acid solution turns yellow as it is evaporated, and leaves a residue insoluble in potassium carbonate: *xanthine*.

b. The nitric acid solution turns dark brown, and leaves a residue soluble in ammonia: *cystine*.

CHAPTER LXXII.

AVERAGE COMPOSITION OF THE NORMAL URINE, FROM TWENTY-FOUR HOURS, OF MEN WEIGHING FROM 60 to 65 KILOS.

Average quantity from 24 hrs., 1400 to 1600 cubic centimetres.		
Average specific gravity,	.	1.020.
Mean amount of solids,	.	55 to 66 grammes.
Urea,	.	30 to 40 "
Uric acid,	.	0.5 "
Xanthine-like alkaloid,	.	undetermined.
Kreatine,	.	0.3 "
Kreatinine,	.	0.45 "
Reducine,	.	undetermined.
Hippuric acid,	.	0.5 "
Indigogen,	.	} undetermined.
Urrhodinogen,	.	
Phenol-producing substance,	.	
Cresol-producing substance,	.	
Chromogen of Urobiline,	.	
Omichmyl-oxyde,	.	}
Urochrome,	.	
Acetic acid,	.	0.288 "
Formic acid,	.	0.05 "
Kryptophanic acid,	.	0.65 "
Carbonic acid,	.	undetermined.
Chlorine,	.	6 to 8 "
Chlorides of sodium and potassium,	.	10 to 13 "
Sulphuric acid,	.	1.5 to 2.5 "
Other sulphur-compounds,	.	{ containing up to 0.2 grm. of sulphur in 24 hrs.
Phosphoric acid,	.	3.66 grammes.
Potassium,	.	} undetermined.
Sodium,	.	
Calcium oxyde,	.	0.17 "
Magnesium oxyde,	.	0.19 "
Earthy phosphates,	.	1.28 "
Iron,	.	undetermined.

Ammonia,	0·7 grammes.
Trimethylamine,	undetermined.
Biliary acids,	0·012 „
Dinitrogenised derivate of sar- colactic acid,	} undetermined.
Oxaluric acid,	
Oxalic acid,	

The minor estimates account for 48 out of 55 grammes of solids, the larger estimates for 62 out of 66 grammes of solids.

I have not in this edition given the tables for the conversion of French weights and measures into English weights and measures which were contained in the first edition, as the principal values showing the relations of these weights and measures to each other are now to be found in the British Pharmacopœia.

INDEX.

- ABSCESSSES**, pus from, 392
Acetone, 488
 in diabetic urine, 489
 mode of obtaining, 488
 observation of, 489
 properties of, 489
Acid, abietinic, 540
 acetic, 247
 baryum salts, 251
 lead salts, 249
 mode of obtaining, 247
 quantity from daily urine, 252
 state in urine, 253
 anisic, 539
 benzoglykolic, 148
 benzoic, 540
 camphoric, 539
 carbolic, 190
 carbonic, 268
 history and literature, 268
 indications, 270
 occurrence, &c., 268
 quantity, 269
 cholic, 418
 cinnamic, 540
 citric, 540
 cuminic, 539
 damaluric, 528
 damolic, 528, 530
 formic, 247
 isomorphism of baryum salt, 252
 lead salt, 249
 mode of obtaining, 247
 quantity from daily urine, 253
 state in urine, 253
 gallic, 535
 glucic, 428
 glykocholic, 416
 hippuric, 144
 hyposulphurous, 293
 baryum salt, 294
 reactions, 294
 kryptophanic, 255
 chemical properties, 258
 compounds, 260
 metamorphoses, 263
 mode of isolating, 255
 without heat, 257
 purification by lead acetate, 256
 by copper acetate, 256
 theoretical consideration, 267
 kynuric, 522
 lactic, 456
 lithuric, 526
 malic, 540
 meconic, 538
 melassic, 428
 oxalic, 500
 oxymandelic, 520
 phenylic, 190
 phosphoric, 303
 salicylic, 537
 salicylous, 538
 salicyluric, 537
 succinic, 533
 sulphuric, 285
 origin, 287
 pathological indications, 29
 precipitable, 286
 quantity in disease, 290
 sulphurous, 293
 in distillates from extracts, 207
 reactions, 294
 tannic, 535
 tartaric, 534
 taurocholic, 417
 taurylic, 539
 toluric, 536
 toluylic, 537
 uric, 56
 urocaninic, 534
Acidity of urine, 5
Albumen, 373
 characters, composition, 376
 diagnosis, 376
 pathological indications, 379
 quantity, 378
 in chylous urine, 369
Albuminuria, 379
Alcohol, 476
 chronic acid test for, 479
 elimination by kidneys, 481
 mode of isolating from organic fluids, 478
 occurrence, 476
 physical and chemical properties, 477
 physiological effects, 481
 social aspect of alcohol, 485
Alkalinity of urine, 7
 causes, 7, 8
 from ammonia formed after discharge, 7
 from decomposition of urea before emission, 8
 inflammation of bladder produced by, 9

- Alkalinity, from fixed alkalis, 11
therapeutic indications, 10
- Alkaloids, 189
- Allantoine, 493
pathological indications, 495
properties, 494
- Ammonia, 313
analysis volumetrical, 314
chemical properties, 314
formation and indications, 313
origin and quantity, 317
- Antimony, 548
copper test, 548
diagnosis from arsenic, 549
- Arsenic, 548
copper test for, 548
diagnosis from antimony, 549
- BILE, acids, 415
colouring matters, 408
composition, 416
in urine, 419, 422
pathological indications, 423
- Bilifuscin, 410
- Bilirubine, 409
- Biliverdine, 410
- Bladder, cancer of, causing hematuria, 350
conditions producing alkaline urine, 9
producing hematuria, 350
producing purulent urine, 392
inflammation of, by alkaline urine, 9
- Blood in urine, 346
chemical diagnosis, 346
coagula, 346
corpuscles, 346
microscopical diagnosis, 347
pathological indications, 349
spectroscopical diagnosis, 348
- CALCIUM, 327
estimation as sulphate, 328
as oxalate, 329
occurrence, 327
phosphate, 327
physical and chemical properties, 327.
- Calculi, alternating, 91
ammonio-magnesian phosphate, 333
cystine, 475
fusible, 333
hemorrhage from, 35
mixed, 91
mulberry, 503
oxalate of lime, 508
phosphate of lime, 333
phosphates, earthy, 333
pistiform, 88
urates, 67, 91
uric acid, 83
uric oxyde, 103
xanthic oxyde, 103
xanthine, 103
- Cancer of bladder, 398
of kidneys, 398
- Cancerous matter in urine, 388
- Casts of uriniferous tubules, 382
epithelial, 383
fatty, 384
granular, 383
hyaloid, 383
- Casts, intratubular, 383
large, 384
small, 383
waxy, 384
- Chloride of potassium, 273
of sodium, 271
detection in urine, 272
- Chlorine in urine, 273
estimation of quantity, 273
quantity in health, 273
in disease, 281
- Cholera, urine in, 188
- Chylous urine, 368
albumen in, 369
fat in, 370
fibrine in, 369
pathological indications, 371
- Collection of urine, 14
- Colouring matter of bile, 409
in urine, 419, 422
of urine, normal, 217
- Copper, 550
test for sugar, 428, 430
- Creosote, reaction of, 202
urine after treatment with, 204
- Cresol, 200
history and literature, 200
mode of obtaining, 201
producing substances, 200
properties, 201
- Cruentine, 357
- Cruenturesis, 358
- Cyanourine, 168
- Cystine, 470
calculi, 475
properties, 471
- Cystiniferous urine, 472
- Cystitis, 9
- Cysticercus teniae echinococcus, 399
- DEXTINE, 450
- Diabetes insipidus, 19
mellitus, urine in, 446
acetone in urine of, 448
- EARTHS, *see* Calcium and Magnesium, 327
- Echinococcus hominis, 399
- FAT in urine, 370, 386
forms of, in chylous urine, 370
pathological indications, 370
- Ferment of urea and urine, 395
- Fermentation, 428
lactic, 429
vinous, 428
viscous, 429
- Fever, urine in, 58
- Fibrine, 368
in chylous urine, 369
- Fibrinous casts, *see* Casts, 382
- Food influence on reaction of urine, 12
on urea, 54
- GLUCOSE, 425
- Glucosides, 425
- Glykokoll, 417
- Grape sugar, 425
volumetric estimation, 430
- Gravel, uric acid, 88

- Gravel, oxalate of lime, 508
 Gravimeter, 23
 Guanine, 115
 characters, physical and chemical, 117
 compounds, 117
 decompositions, 117
 diagnosis, 120
 history and literature, 115
 mode of obtaining, 116
- HEMATINE, 352, 355
 spectral phenomena, 355
 Hematocrystalline, 352
 spectral phenomena, 353
 pathological indications, 361
 Hematuria, intermittent, 358
 spectrum of urine in, 360
 Hemorrhoids of bladder, 350
 Hemorrhage from bladder, 350
 from kidneys, 349
 Herbivora, urine of, 146, 526, 528
 Hippurate of baryum, 150
 calcium, 150
 iron, 150
 lead, 150
 Hippuric acid, 144
 chemical and physical properties, 147
 compounds, 149
 decompositions, 147
 deposits, 165
 history and literature, 144
 means of procuring, 145
 occurrence, 144
 pathological, 162
 physiology, 151
 quantity, 156
 salts, 150
 variations of quantity, 159
 Hydrosulphocyanic acid, 298
 Hydrothion, 298
 Hydruria, 27
 Hypoxanthine, 107
 characters, physical and chemical, 109
 compounds, 110
 deposits of, 112
 diagnosis, 120
 history and literature, 107
 mode of obtaining, 107
 symptom of disease, 112
- INDICAN, 175
 Indigo blue, 174
 identity with uroglauine, 168
 metamorphoses, 177
 modes of obtaining, 176
 brown, 176
 glue, 176
 red, 176
 white, 176
 Indigogen, 167
 choleraic, 183
 estimation of quantity, 181
 introduction and literature, 167
 mode of isolating, 170
 quantity secreted, 181
 variations in disease, 183
 Indol, 177
 Inosite, 452
 in diabetic urine, 454
- Inosite, properties, 453
 Iodine, 551
 volumetrical estimation, 552
 Iron, 341
 estimation, 343
 physiology, 344
 Isatine, 177
- KIDNEYS, cancer of, 349
 diseases of, indicated by albuminous urine, 379
 indicated by blood in urine, 349
 by casts, 384
 by pus, 391
 tubercle of, 393
 Kreatine, 123
 chemical properties, 130
 decompositions, 131
 history, 122
 modes of obtaining, 123
 occurrence, 122
 physical properties, 130
 physiology, 133
 quantity in time, 133
 tables of, 137
 Kreatinine, 122
 chemical properties, 125
 compounds, 126
 modes of obtaining, 123, 124
 quantity in time, 134
 tables of, 137
 Kynuric acid, 522
- LACTATES, 462
 Lactic acid, 456
 compounds, 462
 mode of obtaining, 456
 from urine, 459
 pathological indications, 465
 polarising phenomena, 463
 properties, 460
 Lactide, 460
 Lead, 549
 Leucine, 511, 512
 compounds, 514
 history and occurrence, 511
 production, 511
 from urine, 518
 properties, 513
 Lime, *see* Calcium, 327
 oxalate, *see* Oxalate, 508
 phosphate, *see* Phosphate, 304
 Lithuric acid, 526
- MAGNESIUM, 326
 phosphate, 326
 physiological quantity, 337
 table of, 337
- Melanine, 231
 Mercury, 550
 Metauropittine, 245
 Morphine, 544
 Mucus, 388
 excess of, 389
 pathological indications, 389
 Murexide, 62
 Muscle, hypoxanthine in, 108
 kreatine in, 123
 kreatinine in, 124

- Muscle, lactic acid in, 456
- ODOUR of urine, 5
- Oil, essential of urine, 223
- Omicolic acid, 233
- Omicoline, 233
 chemical properties, 239
 elementary composition, 241
 formula, 242
 mode of obtaining, 238
 mode of separating from each other, 239
 purification, 239
 spectra of, 240
- Omicinyl-oxyde, 210
 chemical characters, 210
 history and preparation, 210
- Oxalate of lime, 308
 calculi, 508
 statistics, 510
 crystallisation, 502
 pathological indications, 503
 polarisation, 502
- Oxalic acid, 500
 compounds, 501
 estimation in urine, 503
 history and occurrence, 500
 mode of obtaining, 501
 pathological indications, 503
 properties, 501
 reappearance in urine, 505
- Oxaluria, case of, 504
- Oxaluric acid, 497
 relations of, 498
- Oxyde, uric, 94
 xanthic, 94
- Oxymandelic acid, 520
- PARAMELANINE, 237
 spectrum of sulphate of, 238
- Phenol or carbolic acid, 190
 bearing in body of animals, 196
 chemical properties, 191
 history and literature, 190
- Phenol-producing substances, 190
 presence in human urine, 191
 in horses' urine, 192
- Phenol-sulphuric acid, 193
- Phosphate of calcium, 304, 327
 calculi, 333
 deposits, 331
 pathological indications, 338
 of magnesium, 327
 ammonio, 332
 calculi, 333
 deposits, 332
 pathological indications, 338
 of potassium, 326
 of sodium, 326
- Phosphates, alkaline, 304
 earthy, 304
 calculi, 333
 deposits, 330
 pathological indications, 338
 physiological quantities, 336
- Phosphoric acid, 303
 volumetric estimation, 307
 estimation in alkalis and earths separately, 303
 physical and chemical properties, 303
- Phosphoric acid, physiology, 310
 quantity in health, 303
 in disease, 311
 salts, 304
- Pigments, abnormal, 3; *see also* Urrery-thrine, 212
 indigogen, 167
- Pneumonia, urine in, 54
- Polarisation of diabetic urine, 431
 of oxalate of lime, 502
- Potassium, 321
 analysis, 323
 chloride 325
 physiological relations, 323
 sulphate, 325
 phosphate, 326
- Purpurine, *see* Urrhodine, 177
- Pus, 390
 casts, 391
 globules, 390
 pathological indications, 391
- Pycnometer, 22
- Pyrocatechin, 187
 chemical characters, 188
 diagnosis and significance, 189
 history and literature, 187
 mode of extracting from urine, 187
- QUINIDINE, 541
- Quinine, 541
 tests for, 542
- REACTION of urine, 5
 substances causing, 6
- Reducine, 139.
 baryum compound, 140
 composition, 141
 history and literature, 139
 isolation with other alkaloids, 139
- Rheumatic fever, urine in, 216
- SACCHARIMETRY, optical, 431
 volumetrical, 430
- Salts, inorganic, *see* Potassium, Sodium, Magnesium, Calcium, &c.
 urophanic, 548
- Santonine, 544
- Sarcina ventriculi, 407
- Sarkine, 107
- Sarkolactic acid, *see* Lactic acid, 456
 dinitrogenised derivat of, 467
- Sodium analysis, 323
 chloride, 325
 phosphate 326
 physiological relations, 323
 sulphate, 325
- Solids in urine, 20
 calculation from specific gravity, 24
- Specific gravity of urine, 20
- Spermatozoa, 405
 detection of, 405
 indications, 406
- Stone, *see* Calculi
- Strychnine, 543
- Sugar, grape, 425
 estimation, optical, 431
 volumetrical, 430
 compounds, 427
 decompositions, 437

- Sugar, mode of obtaining, 425
 pathological indications, 446
- Sulphocyanic acid, 298
 lead salt, 300
 new reaction for, 300
- Sulphur in organic compound in urine, 286
 mode of showing presence, 286
 mode of estimating quantity, 286, 295
 physiology of different forms, 300
 in cystine, 470
 in taurine, 418
- Sulphuric acid, 285
 origin, 287
 pathological indications, 290
 precipitable, 296
 quantity in disease, 290
- Sulphurous acid, 293
 in distillates from extracts, 297
 reactions, 294
- T**
- T***ENIA* echinococcus, 399
- Tar treatment, urine after, 204
- Tartaric acid, 534
 urophanic, 534
- Tartrates, 534
- Taste of urine, 5
- Taurine, 418
- Tobacco, ammonia from, 317
- Trimethylamine, 319
- Tubercular matter, 398
- Tubules, casts of uriniferous, *see* Casts, 382
- Turbidity of urine, 1
- Tyrosine, 511, 515
 production, 511
 properties, 515
- U**
- UROHEMATINE**, 361, 363
 Uremia, 55
- Urate of ammonia, 65
 lime, 66
 potash, 66
 soda, 65
- Urates, calculi of, 67, 91
 do. with layers of uric acid, 91
 deposits, 67
 after emission, 67, 78
 in urinary organs, 79
 diagnosis of, 68
- Urea, 29
 analysis, quantitative, 46
 Bunsen's, 35
 Davy's, 36
 Liebig's, 38
 other methods, 36
 chemical properties, 34
 combinations, 36
 with sodic chloride, 37
 mercuric nitrate, 37
 nitric acid, 37
 oxalic acid, 37
 mercuric oxide, 36
 decompositions, 34
 definition, Boerhaave's, 30
 detection, 33
 diminution, 55
 excess, 54
 history, 29
 occurrence in blood and tissues, 31
 physical properties, 34
- Urea, quantity in health, 53
 in disease, 54
 retention in blood, 55
 synthesis, 34
- Urerythrine, 212
 diagnosis in urine, 214
 diseases in which it occurs, 216
 history and literature, 212
 mode of obtaining it pure, 212
 pathology of, 215
 physical and chemical properties of, 213
- Uric acid, 56
 amount in health, 75
 in disease, 76
 calculi of, 88
 alternating with urates, 91
 composition, 56
 concretions, 87
 chemical characters of, 90
 crystallography, 60
 deposits, 82
 after emission, 83
 in urinary organs, 79
 gravel, 87
 history, 56
 metamorphoses, 61
 methods of procuring pure, 57
 physical properties, 60
 salts, 65
 sediments, crystallised, 85
- Urinal for hospitals, 14
- Urine, acidity of, 6
 alkaline, 7
 ammoniacal, 7, 8
 chylous, 368
 clear and turbid, 1
 collection of, 14
 odour, 5
 quantity of, in health, 16
 in given times, 16
 in diseases, 18
 solids, 20
 specific gravity, 20
 taste, 5
 tints, 2
- Urobiline, 207
 chromogen of, 207
 introduction to, 207
 mode of obtaining, 207
- Urocaninic acid, 524
- Urochrome, 217
 decompositions, 221
 isolation of, 218
 physical and chemical properties, 220
 purification, 220
- Urofaucohematine, 363, 367
- Urogravimeter, 23
- Uroglaucone, 168
- Uromelanine, 221
 compounds, 225
 elementary composition, 225
 origin and significance, 231
 physical and chemical characters, 224
 quantity excreted, 233
- Urophanic inorganic bodies, 548
 metamorphic products, 546
 organic acids, 532
 bases, 541

- Uropittine, 221, 243
 analyses, 244
 mode of obtaining from urine directly, 222
- Urorubine, 246
- Urorubrohematine, 361, 363
- Urostealith, 387
- Uroxanthine, 168
- Urrhodine, 177, 178
- Urrhodinogen, 167
 introduction and literature, 167
 mode of isolating, 170
- VEGETABLE acids, 532
- Veratrine, 544
- WATER of urine, 20
- Weight of urine of different densities, 22
- XANTHIC oxyde, 94
- Xanthine, 94
 calculi, 103
 compounds, 101
 mode of obtaining, 95
 notes to, 105
 properties, 100
- ZYMOLACTIC acid, *see* Lactic acid, 457.

Catalogue B]

*London, 11, New Burlington Street
August, 1884*

SELECTION

FROM

J. & A. CHURCHILL'S GENERAL CATALOGUE

COMPRISING

ALL RECENT WORKS PUBLISHED BY THEM

ON THE

ART AND SCIENCE OF MEDICINE



N.B.—As far as possible, this List is arranged in the order in which medical study is usually pursued

J. & A. CHURCHILL publish for the following Institutions
and Public Bodies:—

H.M. STATIONERY OFFICE.

VIVISECTION FORMS AND CERTIFICATES.

A to F (6 at $\frac{1}{2}$ d. each). Application for Licence, $\frac{1}{2}$ d.

ROYAL COLLEGE OF SURGEONS.

CATALOGUES OF THE MUSEUM.

Twenty separate Catalogues (List and Prices can be obtained of J. & A. CHURCHILL).

GUY'S HOSPITAL.

REPORTS BY THE MEDICAL AND SURGICAL STAFF.

Vol. XXVI., Third Series (1883). Price 7s. 6d.

LONDON HOSPITAL.

PHARMACOPŒIA OF THE HOSPITAL. 3s.

CLINICAL LECTURES AND REPORTS BY THE MEDICAL AND
SURGICAL STAFF. Vols. I. to IV. 7s. 6d. each.

ST. BARTHOLOMEW'S HOSPITAL.

CATALOGUE OF THE ANATOMICAL AND PATHOLOGICAL
MUSEUM. Vol. I.—Pathology. 15s.

ST. GEORGE'S HOSPITAL.

REPORTS BY THE MEDICAL AND SURGICAL STAFF.

The last Volume (X.) was issued in 1880. Price 7s. 6d.

CATALOGUE OF THE PATHOLOGICAL MUSEUM. 15s.

SUPPLEMENTARY CATALOGUE (1882). 5s.

ST. THOMAS'S HOSPITAL.

REPORTS BY THE MEDICAL AND SURGICAL STAFF.

Annually. Vol. XI., New Series (1882). 7s. 6d.

ROYAL LONDON OPHTHALMIC HOSPITAL.

REPORTS BY THE MEDICAL AND SURGICAL STAFF.

Occasionally. Vol. X., Part III. (August, 1882). 5s.

MEDICO-PSYCHOLOGICAL ASSOCIATION.

JOURNAL OF MENTAL SCIENCE.

Quarterly. Price 3s. 6d. each, or 14s. per annum.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.

PHARMACEUTICAL JOURNAL AND TRANSACTIONS.

Each Week. Price 4d. each, or 20s. per annum, post free.

BRITISH PHARMACEUTICAL CONFERENCE.

YEAR BOOK OF PHARMACY.

In December. Price 10s.

BRITISH DENTAL ASSOCIATION.

JOURNAL OF THE ASSOCIATION AND MONTHLY REVIEW
OF DENTAL SURGERY.

On the 15th of each Month. Price 6d., or 13s. per annum, post free.

A SELECTION

FROM

J. & A. CHURCHILL'S GENERAL CATALOGUE,

COMPRISING

ALL RECENT WORKS PUBLISHED BY THEM ON THE ART AND SCIENCE OF MEDICINE.

N.B.—J. & A. Churchill's *Descriptive List of Works on Chemistry, Materia Medica, Pharmacy, Botany, Photography, Zoology, the Microscope, and other Branches of Science, can be had on application.*

Practical Anatomy :

A Manual of Dissections. By CHRISTOPHER HEATH, Surgeon to University College Hospital. Fifth Edition. Crown 8vo, with 24 Coloured Plates and 269 Engravings, 15s.

Wilson's Anatomist's Vade-

Mecum. Tenth Edition. By GEORGE BUCHANAN, Professor of Clinical Surgery in the University of Glasgow; and HENRY E. CLARK, M.R.C.S., Lecturer on Anatomy at the Glasgow Royal Infirmary School of Medicine. Crown 8vo, with 450 Engravings (including 26 Coloured Plates), 18s.

Braune's Atlas of Topographi-

cal Anatomy, after Plane Sections of Frozen Bodies. Translated by EDWARD BELLAMY, Surgeon to, and Lecturer on Anatomy, &c., at, Charing Cross Hospital. Large Imp. 8vo, with 34 Photolithographic Plates and 46 Woodcuts, 40s.

An Atlas of Human Anatomy.

By RICKMAN J. GODLEE, M.S., F.R.C.S., Assistant Surgeon and Senior Demonstrator of Anatomy, University College Hospital. With 48 Imp. 4to Plates (112 figures), and a volume of Explanatory Text, 8vo, £4 14s. 6d.

Surgical Anatomy :

A series of Dissections, illustrating the Principal Regions of the Human Body. By JOSEPH MACLISE. Second Edition. 52 folio Plates and Text. £3 12s.

Medical Anatomy.

By FRANCIS SIBSON, M.D., F.R.C.P., F.R.S. Imp. folio, with 21 Coloured Plates, 42s.

Anatomy of the Joints of Man.

By HENRY MORRIS, Surgeon to, and Lecturer on Anatomy and Practical Surgery at, the Middlesex Hospital. 8vo, with 44 Lithographic Plates (several being coloured) and 13 Wood Engravings, 16s.

Manual of the Dissection of the

Human Body. By LUTHER HOLDEN, Consulting Surgeon to St. Bartholomew's and the Foundling Hospitals, and JOHN LANGTON, F.R.C.S., Surgeon and Lecturer on Anatomy at St. Bartholomew's Hospital. Fifth Edition. 8vo, with many Engravings. *[In the Press.]*

By the same Author.

Human Osteology.

Sixth Edition, edited by the Author and JAMES SHUTER, F.R.C.S., M.A., M.B., Assistant Surgeon to St. Bartholomew's Hospital. 8vo, with 61 Lithographic Plates and 89 Engravings. 16s.

Also.

Landmarks, Medical and Surgical.

Fourth Edition. 8vo. *[In the Press.]*

The Student's Guide to Surgical

Anatomy : An Introduction to Operative Surgery. By EDWARD BELLAMY, F.R.C.S. and Member of the Board of Examiners. Fcap. 8vo, with 76 Engravings, 7s.

The Student's Guide to Human

Osteology. By WILLIAM WARWICK WAGSTAFFE, late Assistant Surgeon to St. Thomas's Hospital. Fcap. 8vo, with 23 Plates and 66 Engravings, 10s. 6d.

The Anatomical Remembran-

cer ; or, Complete Pocket Anatomist. Eighth Edition. 32mo, 3s. 6d.

Diagrams of the Nerves of the Human Body, exhibiting their Origin, Divisions, and Connections, with their Distribution to the Various Regions of the Cutaneous Surface, and to all the Muscles. By W. H. FLOWER, F.R.S., F.R.C.S. Third Edition, with 6 Plates. Royal 4to, 12s.

Atlas of Pathological Anatomy. By Dr. LANCEREAUX. Translated by W. S. GREENFIELD, M.D., Professor of Pathology in the University of Edinburgh. Imp. 8vo, with 70 Coloured Plates, £5 5s.

A Manual of Pathological Anatomy. By C. HANDFIELD JONES, M.B., F.R.S., and E. H. SIEVERING, M.D., F.R.C.P. Edited by J. F. PAYNE, M.D., F.R.C.P., Lecturer on General Pathology at St. Thomas's Hospital. Second Edition. Crown 8vo, with 195 Engravings, 16s.

Lectures on Pathological Anatomy. By S. WILKS, M.D., F.R.S., and W. MOXON, M.D., Physician to Guy's Hospital. Second Edition. 8vo, Plates, 18s.

Post-mortem Examinations: A Description and Explanation of the Method of Performing them, with especial reference to Medico-Legal Practice. By Prof. VIRCHOW. Translated by Dr. T. P. SMITH. Second Edition. Fcap. 8vo, with 4 Plates, 3s. 6d.

The Human Brain:

Histological and Coarse Methods of Research. A Manual for Students and Asylum Medical Officers. By W. BEVAN LEWIS, L.R.C.P. Lond., Deputy Medical Superintendent to the West Riding Lunatic Asylum. 8vo, with Wood Engravings and Photographs, 8s.

Manual of Physiology:

For the use of Junior Students of Medicine. By GERALD F. YEO, M.D., F.R.C.S., Professor of Physiology in King's College, London. Crown 8vo, with 300 Engravings, 14s.

Principles of Human Physiology. By W. B. CARPENTER, C.B., M.D., F.R.S. Ninth Edition. By HENRY POWER, M.B., F.R.C.S. 8vo, with 3 Steel Plates and 377 Wood Engravings, 31s. 6d.

Sanderson's Handbook for the Physiological Laboratory. By E. KLEIN, M.D., F.R.S.; J. BURDON-SANDERSON, M.D., F.R.S.; MICHAEL FOSTER, M.D., F.R.S.; and T. LAUDER BRUNTON, M.D., F.R.S. 8vo, with 123 Plates, 24s.

Histology and Histo-Chemistry of Man. By HEINRICH FREY, Professor of Medicine in Zurich. Translated by ARTHUR E. J. BARKER, Assistant Surgeon to University College Hospital. 8vo, with 608 Engravings, 21s.

A Treatise on Human Physiology. By JOHN C. DALTON, M.D. Seventh Edition. 8vo, with 252 Engravings, 20s.

The Law of Sex.

By G. B. STARKWEATHER, F.R.G.S. With 40 Illustrative Portraits. 8vo, 16s.

The Marriage of Near Kin,

Considered with respect to the Laws of Nations, Results of Experience, and the Teachings of Biology. By ALFRED H. HUTH. 8vo, 14s.

Medical Jurisprudence:

Its Principles and Practice. By ALFRED S. TAYLOR, M.D., F.R.C.P., F.R.S. Third Edition, by THOMAS STEVENSON, M.D., F.R.C.P., Lecturer on Medical Jurisprudence at Guy's Hospital. 2 vols. 8vo, with 188 Engravings, 31s. 6d.

By the same Author.

A Manual of Medical Jurisprudence. Tenth Edition. Crown 8vo, with 55 Engravings, 14s.

Also.

Poisons,

In Relation to Medical Jurisprudence and Medicine. Third Edition. Crown 8vo, with 104 Engravings, 16s.

Lectures on Medical Jurisprudence. By FRANCIS OGSTON, M.D., late Professor in the University of Aberdeen. Edited by FRANCIS OGSTON, Jun., M.D. 8vo, with 12 Copper Plates, 18s.

A Handy Book of Forensic Medicine and Toxicology. By C. MEYMOTT TIDY, M.D., F.C.S., and W. BATHURST WOODMAN, M.D., F.R.C.P. 8vo, with 8 Lithographic Plates and 116 Engravings, 31s. 6d.

Microscopical Examination of Drinking Water and of Air. By J. D. MACDONALD, M.D., F.R.S., Ex-Professor of Naval Hygiene in the Army Medical School. Second Edition. 8vo, with 25 Plates, 7s. 6d.

Sanitary Examinations

Of Water, Air, and Food. A Vade-Mecum for the Medical Officer of Health. By CORNELIUS B. FOX, M.D., F.R.C.P. Crown 8vo, with 94 Engravings, 12s. 6d.

Dangers to Health:

A Pictorial Guide to Domestic Sanitary Defects. By T. PRIDGIN TEALE, M.A., Surgeon to the Leeds General Infirmary. Fourth Edition. 8vo, with 70 Lithograph Plates (mostly coloured), 10s.

Dress: Its Sanitary Aspect.

A Paper read before the Brighton Social Union, Jan. 30, 1880. By BERNARD ROTH, F.R.C.S. 8vo, with 8 Plates, 2s.

How to Arrest Infectious Diseases. By EDGAR G. BARNES, M.D. Lond., Medical Officer of Health of the Eye Urban and Hartismere Rural Sanitary Districts. Fcap. 8vo, 2s. 6d.

A Manual of Practical Hygiene.

By F. A. PARKES, M.D., F.R.S. Sixth Edition, by F. DE CHAUMONT, M.D., F.R.S., Professor of Military Hygiene in the Army Medical School. 8vo, with numerous Plates and Engravings. 18s.

A Handbook of Hygiene and Sanitary Science.

By GEO. WILSON, M.A., M.D., F.R.S.E., Medical Officer of Health for Mid-Warwickshire. Fifth Edition. Crown 8vo, with Engravings, 10s. 6d.

By the same Author.

Healthy Life and Healthy Dwellings:

A Guide to Personal and Domestic Hygiene. Fcap. 8vo, 5s.

Hospitals, Infirmarys, and Dispensaries:

Their Construction, Interior Arrangement, and Management; with Descriptions of existing Institutions, and 74 Illustrations. By F. OPPERT, M.D., M.R.C.P.L. Second Edition. Royal 8vo, 12s.

Pay Hospitals and Paying

Wards throughout the World. By HENRY C. BURDETT, late Secretary to the Seamen's Hospital Society. 8vo, 7s.

By the same Author.

Cottage Hospitals—General,

Fever, and Convalescent: Their Progress, Management, and Work. Second Edition, with many Plans and Illustrations. Crown 8vo, 14s.

Hospital Construction and

Management. By F. J. MOUAT, M.D., Local Government Board Inspector, and H. SAXON SNELL, Fell. Roy. Inst. Brit. Architects. In 2 Parts, 4to, 15s. each; or, the whole work bound in half calf, with large Map, 54 Lithographic Plates, and 27 Woodcuts, 35s.

Manual of Anthropometry:

A Guide to the Measurement of the Human Body, containing an Anthropometrical Chart and Register, a Systematic Table of Measurements, &c. By CHARLES ROBERTS, F.R.C.S. 8vo, with numerous Illustrations and Tables, 8s. 6d.

By the same Author.

Detection of Colour-Blindness

and Imperfect Eyesight. 8vo, with a Table of Coloured Wools, and Sheet of Test-types, 5s.

A Manual of Psychological

Medicine. With an Appendix of Cases. By JOHN C. BUCKNILL, M.D., F.R.S., and D. HACK TUKE, M.D., F.R.C.P. Fourth Edition. 8vo, with 12 Plates (30 Figures) and Engravings, 25s.

Idiocy and Imbecility.

By W. W. IRELAND, M.D., late Medical Superintendent of the Scottish National Institution for Imbecile Children, Larbert, N.B. 8vo, with Engravings, 14s.

Illustrations of the Influence of

the Mind upon the Body in Health and Disease: Designed to elucidate the Action of the Imagination.

By DANIEL HACK TUKE, M.D., F.R.C.P., LL.D. Second Edition. 2 vols. crown 8vo, 15s.

By the same Author.

Sleep-Walking and Hypnotism.

8vo, 5s.

A Manual of Psychological Medi-

cine and Allied Nervous Disorders. By EDWARD C. MANN, M.D., Member of the New York Medico-Legal Society. With Plates. 8vo, 24s.

Mental Diseases.

Clinical Lectures. By T. S. CLOUSTON, M.D., F.R.C.P. Edin., Lecturer on Mental Diseases in the University of Edinburgh. With 8 Plates (6 Coloured). Crown 8vo, 12s. 6d.

Madness:

In its Medical, Legal, and Social Aspects. Lectures by EDGAR SHEPPARD, M.D., M.R.C.P., Professor of Psychological Medicine in King's College. 8vo, 6s. 6d.

The Student's Guide to the

Practice of Midwifery. By D. LLOYD ROBERTS, M.D., F.R.C.P., Physician to St. Mary's Hospital, Manchester. Third Edition. Fcap. 8vo, with 2 Coloured Plates and 127 Wood Engravings, 7s. 6d.

Handbook of Midwifery for Mid-

wives: From the Official Handbook for Prussian Midwives. By J. E. BURTON, L.R.C.P. Lond., Senior Assistant Medical Officer, Ladies' Charity, &c., Liverpool. With Engravings. Fcap. 8vo, 6s.

Lectures on Obstetric Opera-

tions: Including the Treatment of Hæmorrhage, and forming a Guide to the Management of Difficult Labour. By ROBERT BARNES, M.D., F.R.C.P., Obstetric Physician to St. George's Hospital. Third Edition. 8vo, with 124 Engravings, 18s.

By the same Author.

A Clinical History of Medical

and Surgical Diseases of Women. Second Edition. 8vo, with 181 Engravings, 28s.

Clinical Lectures on Diseases

of Women: Delivered in St. Bartholomew's Hospital, by J. MATTHEWS DUNCAN, M.D., F.R.C.P., F.R.S.E. Second Edition. 8vo, 14s.

By the same Author.

Sterility in Woman.

Being the Gulstonian Lectures, delivered in the Royal College of Physicians, Feb., 1883. 8vo, 6s.

The Student's Guide to the Diseases of Women. By ALFRED L. GALABIN, M.D., F.R.C.P., Obstetric Physician to Guy's Hospital. Third Edition. Fcap. 8vo, with 78 Engravings, 7s. 6d.

West on the Diseases of Women. Fourth Edition, revised by the Author, with numerous Additions by J. MATTHEWS DUNCAN, M.D., F.R.C.P., F.R.S.E., Obstetric Physician to St. Bartholomew's Hospital. 8vo, 16s.

Notes on Diseases of Women: Specially designed to assist the Student in preparing for Examination. By J. J. REYNOLDS, L.R.C.P., M.R.C.S. Second Edition. Fcap. 8vo, 2s. 6d.

By the same Author.

Notes on Midwifery:

Specially designed for Students preparing for Examination. Fcap. 8vo, 4s.

Dysmenorrhœa, its Pathology and Treatment. By HEYWOOD SMITH, M.D. Oxon., Physician to the Hospital for Women, &c. Crown 8vo, with Engravings, 4s. 6d.

Obstetric Aphorisms:

For the Use of Students commencing Midwifery Practice. By JOSEPH G. SWAYNE, M.D. Seventh Edition. Fcap. 8vo, with Engravings, 3s. 6d.

Obstetric Medicine and Surgery: Their Principles and Practice. By F. H. RAMSBOTHAM, M.D., F.R.C.P. Fifth Edition. 8vo, with 120 Plates, 22s.

A Complete Handbook of Obstetric Surgery: Giving Short Rules of Practice in every Emergency. By CHARLES CLAY, late Surgeon to St. Mary's Hospital, Manchester. Third Edition. Fcap. 8vo, with 91 Engravings, 6s. 6d.

Schroeder's Manual of Midwifery, including the Pathology of Pregnancy and the Puerperal State. Translated by CHARLES H. CARTER, B.A., M.D. 8vo, with Engravings, 12s. 6d.

Influence of Posture on Women in Gynecic and Obstetric Practice. By J. H. AVELING, M.D., Physician to the Chelsea Hospital for Women. 8vo, 6s.

By the same Author.

The Chamberlens and the Midwifery Forceps: Memorials of the Family, and an Essay on the Invention of the Instrument. 8vo, with Engravings, 7s. 6d.

A Handbook of Uterine Therapeutics, and of Diseases of Women. By E. J. TILT, M.D., M.R.C.P. Fourth Edition. Post 8vo, 10s.

By the same Author.

The Change of Life

In Health and Disease: A Clinical Treatise on the Diseases of the Nervous System incidental to Women at the Decline of Life. Fourth Edition. 8vo, 10s. 6d.

Ovarian and Uterine Tumours:

Their Pathology and Surgical Treatment. By Sir T. SPENCER WELLS, Bart., F.R.C.S., Consulting Surgeon to the Samaritan Hospital. 8vo, with Engravings, 21s.

The Principles and Practice of Gynæcology. By THOMAS ADDIS EMMET, M.D., Surgeon to the Woman's Hospital, New York. Second Edition. Royal 8vo, with 133 Engravings, 24s.

Diseases of the Uterus, Ovaries, and Fallopian Tubes: A Practical Treatise by A. COURT, Professor of Clinical Surgery, Montpellier. Translated from Third Edition by his Pupil, AGNES McLAREN, M.D., M.K.Q.C.P.I., with Preface by J. MATTHEWS DUNCAN, M.D., F.R.C.P. 8vo, with 424 Engravings, 24s.

Backward Displacements of the Uterus and Prolapsus Uteri: Treatment by the New Method of Shortening the Round Ligaments. By WILLIAM ALEXANDER, M.D., M.Ch.Q.U.I., F.R.C.S., Surgeon to the Liverpool Infirmary. Crown 8vo, with Engravings, 3s. 6d.

Chronic Disease of the Heart: Its Bearings upon Pregnancy, Parturition, and Childbed. By ANGUS MACDONALD, M.D., F.R.S.E., Physician to the Edinburgh Royal Infirmary. 8vo, with Engravings, 8s. 6d.

The Female Pelvic Organs:

Their Surgery, Surgical Pathology, and Surgical Anatomy. In a Series of Coloured Plates taken from Nature; with Commentaries, Notes, and Cases. By HENRY SAVAGE, M.D., F.R.C.S., Consulting Officer of the Samaritan Free Hospital. Fifth Edition. Roy. 4to, with 17 Lithographic Plates (15 coloured) and 52 Woodcuts, £1 15s.

The Wasting Diseases of Infants and Children. By EUSTACE SMITH, M.D., Physician to the King of the Belgians, Physician to the East London Hospital for Children. Fourth Edition. Post 8vo, 8s. 6d.

By the same Author.

Clinical Studies of Disease in Children. Second Edition. Post 8vo. [In the Press.]

Infant Feeding and its Influence on Life; or, The Causes and Prevention of Infant Mortality. By C. H. F. ROUTH, M.D., Senior Physician to the Samaritan Hospital. Third Edition. Fcap. 8vo, 7s. 6d.

A Practical Manual of the Diseases of Children. With a Formulary. By EDWARD ELLIS, M.D. Fourth Edition. Crown 8vo, 10s.

By the same Author.

A Manual of what every Mother should know. Fcap. 8vo, 1s. 6d.

A Treatise on the Diseases of Children. For Practitioners and Students. By W. H. DAY, M.D., Physician to the Samaritan Hospital for Women and Children. Crown 8vo, 12s. 6d.

A Manual for Hospital Nurses and others engaged in Attending on the Sick. By EDWARD J. DOMVILLE, Surgeon to the Exeter Lying-in Charity. Fourth Edition. Crown 8vo, 2s. 6d.

A Manual of Nursing, Medical and Surgical. By CHARLES J. CULLINGWORTH, M.D., Physician to St. Mary's Hospital, Manchester. Fcap. 8vo, 3s. 6d.

By the same Author.

A Short Manual for Monthly Nurses. Fcap. 8vo, 1s. 6d.

Notes on Fever Nursing.

By J. W. ALLAN, M.B., Superintendent and Physician, Glasgow Fever Hospital. Crown 8vo, with Engravings, 2s. 6d.

Manual of Botany:

Including the Structure, Functions, Classification, Properties, and Uses of Plants. By ROBERT BENTLEY, Professor of Botany in King's College and to the Pharmaceutical Society. Fourth Edition. Crown 8vo, with 1,185 Engravings, 15s.

By the same Author.

The Student's Guide to Structural, Morphological, and Physiological Botany. With 660 Engravings. Fcap. 8vo, 7s. 6d.

Also.

The Student's Guide to Systematic Botany, including the Classification of Plants and Descriptive Botany. Fcap. 8vo, with 350 Engravings, 3s. 6d.

Medicinal Plants:

Being descriptions, with original figures, of the Principal Plants employed in Medicine, and an account of their Properties and Uses. By Prof. BENTLEY and Dr. H. TRIMEN. In 4 vols., large 8vo, with 306 Coloured Plates, bound in Half Morocco, Gilt Edges, £11 11s.

Royle's Manual of Materia Medica and Therapeutics. Sixth Edition. By JOHN HARLEY, M.D., Physician to St. Thomas's Hospital. Crown 8vo, with 139 Engravings, 15s.

Therapeutical Remembrancer.

By JOHN MAYNE, M.D. Second Edition. 16mo, 3s. 6d.

By the same Author.

Notes on Poisons.

Mounted and Varnished for the Surgery. 18 in. by 12 in. 1s. 6d.

The National Dispensatory:

Containing the Natural History, Chemistry, Pharmacy, Actions and Uses of Medicines. By ALFRED STILLÉ, M.D., LL.D., and JOHN M. MAISCH, Ph.D. Second Edition. 8vo, with 239 Engravings, 34s.

The Student's Guide to Materia Medica and Therapeutics. By JOHN C. THOROWGOOD, M.D., F.R.C.P. Second Edition. Fcap. 8vo, 7s.

Materia Medica and Therapeutics. By CHARLES D. F. PHILLIPS, M.D., F.R.S. Edin., late Lecturer on Materia Medica and Therapeutics at the Westminster Hospital Medical School.

Vol. 1—Vegetable Kingdom. 8vo, 15s.

Vol. 2—Inorganic Substances. 8vo, 21s.

Binz's Elements of Therapeutics: A Clinical Guide to the Action of Drugs. Translated by E. I. SPARKS, M.B., F.R.C.P. Crown 8vo, 8s. 6d.

Materia Medica.

A Manual for the use of Students. By ISAMBARD OWEN, M.D., Lecturer on Materia Medica, &c., to St. George's Hospital. Crown 8vo, 6s.

The Pharmacopœia of the London Hospital. Compiled under the direction of a Committee appointed by the Hospital Medical Council. Fcap. 8vo, 3s.

A Companion to the British Pharmacopœia. By PETER SQUIRE, F.L.S., assisted by his Sons, P. W. and A. H. SQUIRE. 13th Edition. 8vo, 10s. 6d.

By the same Authors.

The Pharmacopœias of the London Hospitals, arranged in Groups for Easy Reference and Comparison. Fifth Edition. 18mo. [*In the Press.*]

Bazaar Medicines of India,

And Common Medical Plants: With Full Index of Diseases, indicating their Treatment by these and other Agents procurable throughout India, &c. By E. J. WARING, C.I.E., M.D., F.R.C.P. Fourth Edition. Fcap. 8vo, 5s.

Tropical Dysentery and Chronic Diarrhœa—Liver Abscess—Malarial Cachexia—Insolation—with other forms of Tropical Diseases, &c. By Sir JOSEPH FAYRER, K.C.S.I., M.D. 8vo, 15s.

By the same Author.

Climate and Fevers of India, with a series of Cases (Croonian Lectures, 1882). 8vo, with 17 Temperature Charts, 12s.

Family Medicine for India.

A Manual. By WILLIAM J. MOORE, M.D., C.I.E., Honorary Surgeon to the Viceroy of India. Published under the Authority of the Government of India. Fourth Edition. Post 8vo, with 64 Engravings, 12s.

By the same Author.

Health-Resorts for Tropical Invalids, in India, at Home, and Abroad. Post 8vo, 5s.

Diseases of Tropical Climates, And their Treatment: With Hints for the Preservation of Health in the Tropics. By JAMES A. HORTON, M.D., Surgeon-Major. Second Edition. Post 8vo, 12s. 6d.

Spirillum Fever

(Synonyms, Famine or Relapsing Fever), as seen in Western India. By H. VANDYKE CARTER, M.D., Surgeon-Major I.M.D. 8vo, with Plates, 21s.

The Student's Guide to the

Practice of Medicine. By MATTHEW CHARTERIS, M.D., Professor of Materia Medica in the University of Glasgow. Third Edition. Fcap. 8vo, with Engravings on Copper and Wood, 7s.

Hooper's Physicians' Vade-

Mecum. A Manual of the Principles and Practice of Physic. Tenth Edition. By W. A. GUY, F.R.C.P., F.R.S., and J. HARLEY, M.D., F.R.C.P. With 118 Engravings. Fcap. 8vo, 12s. 6d.

Clinical Medicine:

Lectures and Essays. By BALTHAZAR FOSTER, M.D., F.R.C.P. Lond., Professor of Medicine in Queen's College, Birmingham. 8vo, 10s. 6d.

Clinical Lectures and Cases,

with Commentaries. By HENRY THOMPSON, M.D., F.R.C.P., Consulting Physician to Middlesex Hospital. With Temperature Charts. 8vo, 7s. 6d.

Clinical Medicine:

A Systematic Treatise on the Diagnosis and Treatment of Disease. By AUSTIN FLINT, M.D., Professor of Medicine in the Bellevue Hospital Medical College. 8vo, 20s.

By the same Author.

Phthisis:

In a series of Clinical Studies. 8vo, 16s.

The Student's Guide to Medical

Diagnosis. By SAMUEL FENWICK, M.D., F.R.C.P., Physician to the London Hospital. Fifth Edition. Fcap. 8vo, with 111 Engravings, 7s.

By the same Author.

The Student's Outlines of Medi-

cal Treatment. Second Edition. Fcap. 8vo, 7s.

Also.

On Chronic Atrophy of the

Stomach, and on the Nervous Affections of the Digestive Organs. 8vo, 8s.

How to Examine the Chest:

Being a Practical Guide for the use of Students. By SAMUEL WEST, M.D., Physician to the City of London Hospital for Diseases of the Chest; Medical Tutor and Registrar at St. Bartholomew's Hospital. With 42 Engravings. Fcap. 8vo, 5s.

The Student's Guide to Medical

Case-Taking. By FRANCIS WARNER, M.D., F.R.C.P., Assistant Physician to the London Hospital. Fcap. 8vo, 5s.

The Microscope in Medicine.

By LIONEL S. BEALE, M.B., F.R.S., Physician to King's College Hospital. Fourth Edition. 8vo, with 86 Plates, 21s. *Also.*

On Slight Ailments:

Their Nature and Treatment. Second Edition. 8vo, 5s.

The Spectroscope in Medicine.

By CHARLES A. MACMUNN, B.A., M.D. 8vo, with 3 Chromo-lithographic Plates of Physiological and Pathological Spectra, and 13 Engravings, 9s.

The Contagiousness of Pulmo-

nary Consumption, and its Anti-septic Treatment. By J. BURNEY YEO, M.D., Physician to King's College Hospital. Crown 8vo, 3s. 6d.

Diseases of the Chest:

Contributions to their Clinical History, Pathology, and Treatment. By A. T. HOUGHTON WATERS, M.D., Physician to the Liverpool Royal Infirmary. Second Edition. 8vo, with Plates, 15s.

The Operative Treatment of In-

tra-thoracic Effusion. Fothergillian Prize Essay. By NORMAN PORRITT, L.R.C.P. Lond., M.R.C.S., late Senior Assistant House-Surgeon, General Infirmary, Leeds; and Senior House-Surgeon, Infirmary, Huddersfield. With Engravings. Crown 8vo, 6s.

Winter Cough

(Catarrh, Bronchitis, Emphysema, Asthma). By HORACE DOBELL, M.D., Consulting Physician to the Royal Hospital for Diseases of the Chest. Third Edition. 8vo, with Coloured Plates, 10s. 6d.

By the same Author.

Loss of Weight, Blood-Spitting,

and Lung Disease. Second Edition, to which is added Part VI., "On the Functions and Diseases of the Liver." 8vo, with Chromo-lithograph, 10s. 6d.

Also.

The Mont Dore Cure, and the

Proper Way to Use it. 8vo, 7s. 6d.

Croonian Lectures on Some

Points in the Pathology and Treatment of Typhoid Fever. By WILLIAM CAYLEY, M.D., F.R.C.P., Physician to the Middlesex and the London Fever Hospitals. Crown 8vo, 4s. 6d.

Diseases of the Heart and Aorta:

Clinical Lectures. By G. W. BALFOUR, M.D., F.R.C.P., F.R.S. Edin., late Senior Physician and Lecturer on Clinical Medicine, Royal Infirmary, Edinburgh. Second Edition. 8vo, with Chromo-lithograph and Wood Engravings, 12s. 6d.

Observations on the Result of

Treatment of nearly One Hundred Cases of Asthma. By T. L. FRIDHAM, M.R.C.S. Third Edition. 8vo, 2s. 6d.

Notes on Asthma :

Its Forms and Treatment. By JOHN C. THOROWGOOD, M.D., Physician to the Hospital for Diseases of the Chest. Third Edition. Crown 8vo, 4s. 6d.

Manual of the Physical Diagnosis of Diseases of the Heart, including the use of the Sphygmograph and Cardiograph. By A. E. SANSOM, M.D., F.R.C.P., Assistant Physician to the London Hospital. Third Edition. Fcap. 8vo, with 48 Engravings, 7s. 6d.

Medical Ophthalmoscopy :

A Manual and Atlas. By WILLIAM R. GOWERS, M.D., F.R.C.P., Assistant Professor of Clinical Medicine in University College, and Senior Assistant Physician to the Hospital. Second Edition, with Coloured Autotype and Lithographic Plates and Woodcuts. 8vo, 18s.

By the same Author.

Epilepsy, and other Chronic Convulsive Diseases : Their Causes, Symptoms, and Treatment. 8vo, 10s. 6d.

Also.

Pseudo-Hypertrophic Muscular Paralysis : A Clinical Lecture. 8vo, with Engravings and Plate, 3s. 6d.

Also.

The Diagnosis of Diseases of the Spinal Cord. Third Edition. 8vo, with Engravings, 4s. 6d.

Studies on Functional Nervous Disorders. By C. HANDFIELD JONES, M.B., F.R.S., Physician to St. Mary's Hospital. Second Edition. 8vo, 18s.

Visceral Neuroses :

Being the Gulstonian Lectures on Neurogia of the Stomach, and Allied Disorders. By T. CLIFFORD ALBUTT, M.A., M.D. Cantab., F.R.S., F.R.C.P., Consulting Physician to the Leeds General Infirmary. 8vo, 4s. 6d.

Nervous Diseases :

Their Description and Treatment. A Manual for Students and Practitioners of Medicine. By ALLEN M. HAMILTON, M.D., Physician at the Epileptic and Paralytic Hospital, New York. Second Edition. Royal 8vo, with 72 Engravings, 16s.

Nerve Vibration and Excitation, as Agents in the Treatment of Functional Disorder and Organic Disease. By J. MORTIMER GRANVILLE, M.D. 8vo, 5s.

Diseases of the Liver :

With and without Jaundice. By GEORGE HARLEY, M.D., F.R.C.P., F.R.S. 8vo, with 2 Plates and 36 Engravings, 21s.

Notes on Rheumatism.

By JULIUS POLLOCK, M.D., F.R.C.P., Senior Physician to the Charing Cross Hospital. Second Edition. Fcap. 8vo, with Engravings, 3s. 6d.

Diseases of the Stomach :

The Varieties of Dyspepsia, their Diagnosis and Treatment. By S. O. HABERSHON, M.D., F.R.C.P. Third Edition. Crown 8vo, 5s.

By the same Author.

Pathology of the Pneumogastric Nerve : Being the Lumleian Lectures for 1876. Post 8vo, 3s. 6d.

Also.

Diseases of the Abdomen,

Comprising those of the Stomach and other parts of the Alimentary Canal, Esophagus, Cæcum, Intestines, and Peritoneum. Third Edition. 8vo, with 5 Plates, 21s.

Gout, Rheumatism,

And the Allied Affections ; with a Chapter on Longevity and the Causes Antagonistic to it. By PETER HOOD, M.D. Second Edition. Crown 8vo, 10s. 6d.

Diseases of the Nervous System.

Clinical Lectures. By THOMAS BUZZARD, M.D., F.R.C.P., Physician to the National Hospital for the Paralysed and Epileptic. With Engravings, 8vo, 15s.

Diseases of the Nervous System.

Lectures delivered at Guy's Hospital. By SAMUEL WILKS, M.D., F.R.S. Second Edition. 8vo, 18s.

A Treatise on the Diseases of the Nervous System. By JAMES ROSS, M.D., F.R.C.P., Assistant Physician to the Manchester Royal Infirmary. Second Edition. 2 vols. 8vo, with Lithographs, Photographs, and 332 Woodcuts, 52s. 6d.

Fits :

Diagnosis and Immediate Treatment of Cases of Insensibility and Convulsions. By JOHN H. WATERS, M.D., K.C.St.G.C., Surgeon to the C Division of Metropolitan Police. Crown 8vo, 4s.

Food and Dietetics,

Physiologically and Therapeutically Considered. By F. W. PAVY, M.D., F.R.S., Physician to Guy's Hospital. Second Edition. 8vo, 15s.

By the same Author.

Croonian Lectures on Certain

Points connected with Diabetes. 8vo, 4s. 6d.

Imperfect Digestion :

Its Causes and Treatment. By A. LEARED, M.D. Seventh Edition. Fcap. 8vo, 4s. 6d.

Headaches :

Their Nature, Causes, and Treatment. By W. H. DAY, M.D., Physician to the Samaritan Hospital. Third Edition. Crown 8vo, with Engravings, 6s. 6d.

Indigestion :

What it is ; What it Leads to ; and a New Method of Treating it. By J. B. GULL, M.D. Third Edition. Fcap. 8vo, 4s. 6d.

On Megrim, Sick Headache, and some Allied Disorders: A Contribution to the Pathology of Nerve Storms. By E. LIVEING, M.D., F.R.C.P. 8vo, 15s.

Nutrition in Health and Disease. By HENRY BENNET, M.D. Third (Library) Edition, 8vo, 5s.; Cheap Edition, fcap. 8vo, 2s. 6d.

The Riviera:

Sketches of the Health-Resorts of the Coast of France and Italy, from Hyères to Spezia: its Medical Aspect and Value, &c. By EDWARD I. SPARKS, M.B., F.R.C.P. Crown 8vo, 8s. 6d.

Winter and Spring

On the Shores of the Mediterranean. By HENRY BENNET, M.D. Fifth Edition. Post 8vo, with numerous Plates, Maps, and Engravings, 12s. 6d.

By the same Author.

Treatment of Pulmonary Consumption by Hygiene, Climate, and Medicine. Third Edition. 8vo, 7s. 6d.

The Principal Southern and Swiss Health-Resorts: their Climate and Medical Aspect. By WILLIAM MARCET, M.D., F.R.C.P., F.R.S. With Illustrations. Crown 8vo, 7s. 6d.

Medical Guide to the Mineral Waters of France and its Wintering Stations. With a Special Map. By A. VINTRAS, M.D., Physician to the French Embassy, and to the French Hospital, London. Crown 8vo, 8s.

The Ocean as a Health-Resort: A Practical Handbook of the Sea, for the use of Tourists and Health-Seekers. By WILLIAM S. WILSON, L.R.C.P. Second Edition, with Chart of Ocean Routes, &c. Crown 8vo, 7s. 6d.

Principal Health-Resorts

Of Europe and Africa, and their Use in the Treatment of Chronic Diseases. By T. M. MADDEN, M.D. 8vo, 10s.

Handbook of Medical and Surgical Electricity. By HERBERT TIBBITS, M.D., F.R.C.P.E., Senior Physician to the West London Hospital for Paralysis and Epilepsy. Second Edition, 8vo, with 95 Engravings, 9s.

By the same Author.

A Map of Ziemssen's Motor Points of the Human Body: A Guide to Localised Electrification. Mounted on Rollers, 35 x 21. With 20 Illustrations, 5s.

Mechanical Exercise a Means of Cure: Being a Description of the Zander Institute, London; its History, Appliances, Scope, and Object. Edited by the Medical Officer of the Institution. Crown 8vo, with 24 Engravings, 2s. 6d.

Ambulance Handbook for Volunteers and Others. By J. ARDAYON RAYE, L.K. & Q.C.P.I., L.R.C.S.I., late Surgeon to H.B.M. Transport No. 14, Zulu Campaign, and Surgeon E.I.R. Rifles. 8vo, with 16 Plates (50 figures), 3s. 6d.

A System of Practical Surgery. By Sir W. FERGUSSON, Bart., F.R.S. Fifth Edition. 8vo, with 463 Engravings, 21s.

Surgical Emergencies:

Together with the Emergencies Attendant on Parturition and the Treatment of Poisoning. By PAUL SWAIN, F.R.C.S., Surgeon to the South Devon and East Cornwall Hospital. Third Edition. Crown 8vo, with 117 Engravings, 5s.

A Course of Operative Surgery. By CHRISTOPHER HEATH, Surgeon to University College Hospital. Second Edition. With 20 Plates, drawn from Nature by M. LÉVEILLÉ, and coloured. Large 8vo, 30s.

By the same Author.

The Student's Guide to Surgical Diagnosis. Second Edition. Fcap. 8vo, 6s. 6d.

Also.

Manual of Minor Surgery and Bandaging. For the use of House-Surgeons, Dressers, and Junior Practitioners. Seventh Edition. Fcap. 8vo, with 129 Engravings, 6s.

Also.

Injuries and Diseases of the Jaws. Third Edition. 8vo, with Plate and 206 Wood Engravings, 14s.

Outlines of Surgery and Surgical Pathology. By F. LE GROS CLARK, F.R.S., assisted by W. W. WAGSTAFFE, F.R.C.S. Second Edition. 8vo, 10s. 6d.

Regional Surgery:

Including Surgical Diagnosis. A Manual for the use of Students. By F. A. SOUTHAM, M.A., M.B., F.R.C.S., Assistant Surgeon to the Manchester Royal Infirmary. Part I. The Head and Neck. Crown 8vo, 6s. 6d. — Part II. The Upper Extremity and Thorax. Crown 8vo, 7s. 6d.

Surgical Enquiries

Including the Hastings Essay on Shock, the Treatment of Inflammations, and numerous Clinical Lectures. By FURNEAUX JORDAN, F.R.C.S., Professor of Surgery, Queen's College, Birmingham. Second Edition, with numerous Plates. Royal 8vo, 12s. 6d.

On Dislocations and Fractures.

By JOSEPH MACLISE, F.R.C.S. Uniform with "Surgical Anatomy." 36 folio Plates and Text. Cloth, £2 10s.

The Practice of Surgery :

A Manual. By THOMAS BRYANT, Surgeon to Guy's Hospital. Fourth Edition. 2 vols. crown 8vo, with nearly 700 Engravings (many being coloured).

The Surgeon's Vade-Mecum :

A Manual of Modern Surgery. By ROBERT DRUITT, F.R.C.S. Eleventh Edition. Fcap. 8vo, with 369 Engravings, 14s.

Illustrations of Clinical Surgery.

By JONATHAN HUTCHINSON, F.R.S., Senior Surgeon to the London Hospital. In occasional fasciculi. I. to XVI., 6s. 6d. each. Fasciculi I. to X. bound, with Appendix and Index, £3 10s.

By the same Author.

Pedigree of Disease :

Being Six Lectures on Temperament, Idiosyncrasy, and Diathesis. 8vo, 5s.

Hernia :

A Practical Treatise. By JOSEPH H. WARREN, M.D. Second Edition. Roy. 8vo, with Plates and 82 Engravings, 21s.

By the same Author.

A Plea for the Cure of Rupture ;

or, The Pathology of the Subcutaneous Operation by Injection. 8vo, with Diagrams, 5s. 6d.

Treatment of Wounds and Frac-

tures. Clinical Lectures. By SAMPSON GAMGEE, F.R.S.E., Surgeon to the Queen's Hospital, Birmingham. Second Edition. 8vo, with 40 Engravings, 10s.

Fractures :

A Treatise. By LEWIS A. STIMSON, B.A., M.D., Professor of Surgical Pathology in the University of New York. 8vo, with 360 Engravings, 21s.

Injuries of the Spine and Spinal

Cord, without Apparent Mechanical Lesion, and NERVOUS SHOCK, in their Surgical and Medico-Legal Aspects. By HERBERT W. PAGE, M.A., M.C. Cantab., F.R.C.S., Surgeon to St. Mary's Hospital. 8vo, 12s. 6d.

Lectures on Orthopædic Surgery.

By BERNARD E. BRODHURST, F.R.C.S., Surgeon to the Royal Orthopædic Hospital. Second Edition. 8vo, with Engravings, 12s. 6d.

By the same Author.

On Anchylosis, and the Treatment for the Removal of De-

formity and the Restoration of Mobility in Various Joints. Fourth Edition. 8vo, with Engravings, 5s.

Also.

Curvatures and Diseases of the

Spine. Third Edition. 8vo, with Engravings, 6s.

The Orthopragms of the Spine :

Curative Mechanisms applicable to Spinal Curvature, &c. By R. HEATHER BIGG, Assoc. Inst. C.E. 8vo, with Engravings, 5s.

Orthopædic Surgery,

And Diseases of the Joints. By L. A. SAYRE, M.D., Professor of Orthopædic Surgery in Bellevue Hospital Medical College. Second Edition. 8vo, with Coloured Plate and 324 Engravings, 21s.

Osteotomy :

With an Enquiry into the Etiology and Pathology of Knock-Knee, Bow-Leg, and other Osseous Deformities of the Lower Limbs. By W. MACEWEN, M.D., Surgeon, &c., to the Glasgow Royal Infirmary. 8vo, with 51 Engravings, 7s. 6d.

Clubfoot :

Its Causes, Pathology, and Treatment. By WM. ADAMS, F.R.C.S., Surgeon to the Great Northern Hospital. Second Edition. 8vo, with 106 Engravings and 6 Lithographic Plates, 15s.

By the same Author.

On Contraction of the Fingers,

and its Treatment by Subcutaneous Operation ; and on Obliteration of Depressed Cicatrices, by the same Method. 8vo, with 30 Engravings, 4s. 6d.

Also.

Lateral and other Forms of

Curvature of the Spine: Their Pathology and Treatment. Second Edition. 8vo, with 5 Lithographic Plates and 72 Wood Engravings, 10s. 6d.

Spinal Curvatures :

Treatment by Extension and Jacket ; with Remarks on some Affections of the Hip, Knee, and Ankle-joints. By H. MACNAUGHTON JONES, M.D., F.R.C.S.I. and Edin. Post 8vo, with 63 Engravings, 4s. 6d.

On Diseases and Injuries of the

Eye: A Course of Systematic and Clinical Lectures to Students and Medical Practitioners. By J. R. WOLFE, M.D., F.R.C.S.E., Lecturer on Ophthalmic Medicine and Surgery in Anderson's College, Glasgow. With 10 Coloured Plates and 157 Wood Engravings. 8vo, £1 1s.

The General Practitioner's

Guide to the Diseases and Injuries of the Eye and Eyelids. By LOUIS H. TOSSWILL, B.A., M.B. Cantab., M.R.C.S., Surgeon to the Exeter Eye Infirmary. Fcap. 8vo, 2s. 6d.

Hintson Ophthalmic Out-Patient

Practice. By CHARLES HIGGINS, Ophthalmic Surgeon to Guy's Hospital. Second Edition. Fcap. 8vo, 3s.

Essays in Ophthalmology.

By GEORGE E. WALKER, F.R.C.S., Surgeon to St. Paul's Eye and Ear Hospital, &c., Liverpool. Post 8vo, 6s.

The Electro-Magnet,

And its Employment in Ophthalmic Surgery. By SIMEON SNELL, Ophthalmic Surgeon to the Sheffield General Infirmary, &c. Crown 8vo, 3s. 6d.

The Student's Guide to Diseases of the Eye. By EDWARD NETTLESHIP, F.R.C.S., Ophthalmic Surgeon to St. Thomas's Hospital. Third Edition. Fcap. 8vo, with 150 Engravings and a Set of Coloured Papers illustrating Colour-Blindness, 7s. 6d.

A Manual of the Principles and Practice of Ophthalmic Medicine and Surgery. By T. WHARTON JONES, F.R.C.S., F.R.S. Third Edition. Fcap. 8vo, with 9 Coloured Plates and 173 Engravings, 12s. 6d.

Glaucoma :

Its Causes, Symptoms, Pathology, and Treatment. By PRIESTLEY SMITH, M.R.C.S., Ophthalmic Surgeon to the Queen's Hospital, Birmingham. 8vo, with Lithographic Plates, 10s. 6d.

Refraction of the Eye :

A Manual for Students. By GUSTAVUS HARTIDGE, F.R.C.S., Assistant Physician to the Royal Westminster Ophthalmic Hospital. Crown 8vo, with Lithographic Plate and 84 Woodcuts, 5s.

Hare-Lip and Cleft Palate.

By FRANCIS MASON, F.R.C.S., Surgeon to St. Thomas's Hospital. 8vo, with 66 Engravings, 6s.

By the same Author.

The Surgery of the Face.

8vo, with 100 Engravings, 7s. 6d.

A Practical Treatise on Aural Surgery. By H. MACNAUGHTON JONES, M.D., Professor of the Queen's University in Ireland, late Surgeon to the Cork Ophthalmic and Aural Hospital. Second Edition. Crown 8vo, with 63 Engravings, 8s. 6d.

By the same Author.

Atlas of Diseases of the Membrana Tympani. In Coloured Plates, containing 62 Figures, with Text. Crown 4to, 21s.

Diseases and Injuries of the Ear. By W. B. DALRY, F.R.C.S., Aural Surgeon to St. George's Hospital. Second Edition. Fcap. 8vo, with Engravings, 6s. 6d.

Lectures on Syphilis of the Larynx (Lesions of the Secondary and Intermediate Stages). By W. M. WHISTLER, M.D., Physician to the Hospital for Diseases of the Throat. Post 8vo, 4s.

Diphtheria :

By PETER FADE, M.D., F.R.C.P., Senior Physician to the Norfolk and Norwich Hospital. 8vo, 3s.

Diseases of the Throat and

Nose : A Manual. By MORELL MACKENZIE, M.D. Lond., Senior Physician to the Hospital for Diseases of the Throat. Vol. I. Diseases of the Pharynx, Larynx, and Trachea. Post 8vo, with 112 Engravings, 12s. 6d.

Vol. II. Diseases of the Nose and Nasopharynx ; with a Section on Diseases of the Oesophagus. Post 8vo, with 93 Engravings, 12s. 6d.

By the same Author.

Diphtheria :

Its Nature and Treatment, Varieties, and Local Expressions. 8vo, 5s.

Sore Throat :

Its Nature, Varieties, and Treatment. By PROSSER JAMES, M.D., Physician to the Hospital for Diseases of the Throat. Fourth Edition. Post 8vo, with Coloured Plates and Engravings, 6s. 6d.

The Ear :

Its Anatomy, Physiology, and Diseases. By C. H. BURNETT, A.M., M.D., Aural Surgeon to the Presbyterian Hospital, Philadelphia. 8vo, with 87 Engravings, 18s.

A Treatise on Vocal Physiology and Hygiene, with especial reference to the Cultivation and Preservation of the Voice. By GORDON HOLMES, M.D., Physician to the Municipal Throat and Ear Infirmary. Second Edition, with Engravings. Crown 8vo, 6s. 6d.

By the same Author.

A Guide to the Use of the Laryngoscope in General Practice. Crown 8vo, with Engravings, 2s. 6d.

A System of Dental Surgery.

By JOHN TOMES, F.R.S., and C. S. TOMES, M.A., F.R.S. Third Edition. Fcap. 8vo, with many Engravings.

[In the Press.]

Dental Anatomy, Human and Comparative: A Manual. By CHARLES S. TOMES, M.A., F.R.S. Second Edition. Crown 8vo, with 191 Engravings, 12s. 6d.

The Student's Guide to Dental Anatomy and Surgery. By HENRY SEWILL, M.R.C.S., L.D.S. Second Edition. Fcap. 8vo, with 78 Engravings, 5s. 6d.

A Manual of Dental Mechanics. By OAKLEY COLES, L.D.S.R.C.S. Second Edition. Crown 8vo, with 140 Engravings, 7s. 6d.

By the same Author.

Deformities of the Mouth.

Third Edition. 8vo, with 83 Wood Engravings and 96 Drawings on Stone, 12s. 6d.

Mechanical Dentistry in Gold and Vulcanite. By F. H. BALKWILL, L.D.S.R.C.S. 8vo, with 2 Lithographic Plates and 57 Engravings, 10s.

Notes on Dental Practice. By HENRY C. QUINBY, L.D.S.R.C.S.I. 8vo, with 87 Engravings, 9s.

Elements of Dental Materia Medica and Therapeutics, with Pharmacopœia. By JAMES STOCKEN, L.D.S.R.C.S., Pereira Prizeman for Materia Medica, and THOMAS GADDES, L.D.S. Eng. and Edin. Third Edition. Fcap. 8vo, 7s. 6d.

Dental Medicine :

A Manual of Dental Materia Medica and Therapeutics. By F. J. S. GORGAS, A.M., M.D., D.D.S., Editor of "Harris's Principles and Practice of Dentistry," Professor in the Dental Department of Maryland University. 8vo, 14s.

Lectures on Dermatology :

Delivered at the Royal College of Surgeons, by Sir ERASMUS WILSON, F.R.S. 1870, 6s. ; 1871-73, 10s. 6d. ; 1874-75, 10s. 6d. ; 1876-78, 10s. 6d.

Eczema.

By MCCALL ANDERSON, M.D., Professor of Clinical Medicine in the University of Glasgow. Third Edition. 8vo, with Engravings, 7s. 6d.

Diseases of the Skin :

With an Analysis of 8,000 Consecutive Cases and a Formulary. By L. D. BULKLEY, M.D., Physician for Skin Diseases at the New York Hospital. Crown 8vo, 6s. 6d.

Atlas of Skin Diseases.

By TILBURY FOX, M.D., F.R.C.P. With 72 Coloured Plates. Royal 4to, half morocco, £6 6s.

On Certain Rare Diseases of the Skin.

By JONATHAN HUTCHINSON, F.R.S., Senior Surgeon to the London Hospital, and to the Hospital for Diseases of the Skin. 8vo, 10s. 6d.

Diseases of the Skin :

A Practical Treatise for the Use of Students and Practitioners. By J. N. HYDE, A.M., M.D., Professor of Skin and Venereal Diseases, Rush Medical College, Chicago. 8vo, with 66 Engravings, 17s.

Parasites :

A Treatise on the Entozoa of Man and Animals, including some Account of the Ectozoa. By T. SPENCER COBOLD, M.D., F.R.S. 8vo, with 85 Engravings, 15s.

Leprosy in British Guiana.

By JOHN D. HILLIS, F.R.C.S., M.R.I.A., Medical Superintendent of the Leper Asylum, British Guiana. Imp. 8vo, with 22 Lithographic Coloured Plates and Wood Engravings, £1 11s. 6d.

Cancer of the Breast.

By THOMAS W. NUNN, F.R.C.S., Consulting Surgeon to the Middlesex Hospital. 4to, with 21 Coloured Plates, £2 2s.

On Cancer :

Its Allies, and other Tumours; with special reference to their Medical and Surgical Treatment. By F. A. PURCELL, M.D., M.C., Surgeon to the Cancer Hospital, Brompton. 8vo, with 21 Engravings, 10s. 6d.

Sarcoma and Carcinoma :

Their Pathology, Diagnosis, and Treatment. By HENRY T. BUTLIN, F.R.C.S., Assistant Surgeon to St. Bartholomew's Hospital. 8vo, with 4 Plates, 8s.

By the same Author.

Malignant Disease of the Larynx (Sarcoma and Carcinoma). 8vo, with 5 Engravings, 5s.

Certain Forms of Cancer,

With a New and Successful Mode of Treating it. By A. MARSDEN, Senior Surgeon to the Cancer Hospital. Second Edition. 8vo, with Coloured Plates, 8s. 6d.

Clinical Notes on Cancer,

Its Etiology and Treatment; with special reference to the Heredity-Fallacy, and to the Neurotic Origin of most Cases of Alveolar Carcinoma. By HERBERT L. SNOW, M.D. Lond., Surgeon to the Cancer Hospital, Brompton. Crown 8vo, 3s. 6d.

Diseases of the Urinary Organs.

Clinical Lectures. By Sir HENRY THOMPSON, F.R.C.S., Emeritus Professor of Clinical Surgery in University College. Seventh (Students') Edition. 8vo, with 84 Engravings, 2s. 6d.

By the same Author.

Diseases of the Prostate :

Their Pathology and Treatment. Fifth (Students') Edition. 8vo, with numerous Engravings, 2s. 6d.

Also.

Practical Lithotomy and Lithotripsy; or, An Inquiry into the Best Modes of Removing Stone from the Bladder. Third Edition. 8vo, with 87 Engravings, 10s.

Also.

The Preventive Treatment of Calculous Disease, and the Use of Solvent Remedies. Second Edition. Fcap. 8vo, 2s. 6d.

Also.

Tumours of the Bladder :

Their Nature, Symptoms, and Surgical Treatment. 8vo, with numerous Illustrations, 5s.

Diseases of the Testis, Spermatic Cord, and Scrotum.

By THOMAS B. CURLING, F.R.S., Consulting Surgeon to the London Hospital. Fourth Edition. 8vo, with Engravings, 16s.

Hæmorrhoidal Disorder.

By JOHN GAY, F.R.C.S., Senior Surgeon to the Great Northern Hospital. 8vo, with Engravings, 2s. 6d.

Hydrocele :

Its several Varieties and their Treatment. By SAMUEL OSBORN, late Surgical Registrar to St. Thomas's Hospital. Fcap. 8vo, with Engravings, 3s.

By the same Author.

Diseases of the Testis.

Fcap. 8vo, with Engravings, 3s. 6d.

Lithotomy and Extraction of

Stone. By W. P. HARRIS, M.D., Surgeon-Major H.M. Bengal Medical Service. 8vo, with Engravings, 10s. 6d.

Fistula, Hæmorrhoids, Painful

Ulcer, Stricture, Prolapsus, and other Diseases of the Rectum : Their Diagnosis and Treatment. By WILLIAM ALLINGHAM, Surgeon to St. Mark's Hospital for Fistula. Fourth Edition. 8vo, with Engravings, 10s. 6d.

The Surgery of the Rectum.

By HENRY SMITH, Professor of Surgery in King's College, Surgeon to the Hospital. Fifth Edition. 8vo, 6s.

Cancer of the Rectum :

Its Pathology, Diagnosis, and Treatment. By W. HARRISON CRIPPS, F.R.C.S., Assistant Surgeon to St. Bartholomew's Hospital, &c. Crown 8vo, with Lithographic Plates, 6s.

Lectures on the Surgical Disorders of the Urinary Organs.

By REGINALD HARRISON, F.R.C.S., Surgeon to the Liverpool Royal Infirmary. Second Edition, with 48 Engravings. 8vo, 12s. 6d.

By the same Author.

Lithotomy, Lithotripsy, and the

Early Detection of Stone in the Bladder ; with a description of a New Method of Tapping the Bladder. 8vo, with Engravings, 2s. 6d.

Morbid Conditions of the Urine,

Dependent upon Derangements of Digestion. By CHARLES H. RALFE, M.D., F.R.C.P., Assistant Physician to the London Hospital. Crown 8vo, 6s.

Renal and Urinary Diseases.

Clinical Reports. By WILLIAM CARTER, M.B., Physician to the Liverpool Southern Hospital. Crown 8vo, 7s. 6d.

Pathology of the Urine.

Including a Complete Guide to its Analysis. By J. L. W. THUDICHUM, M.D., F.R.C.P. Second Edition, rewritten and enlarged. 8vo, with Engravings, 15s.

Student's Primer on the Urine.

By J. TRAVIS WHITTAKER, M.D., Clinical Demonstrator at the Royal Infirmary, Glasgow. With 16 Plates etched on Copper. Post 8vo, 4s. 6d.

Syphilis and Pseudo-syphilis.

By ALFRED COOPER, F.R.C.S., Surgeon to the Lock Hospital, to St. Mark's and the West London Hospitals. 8vo, 10s. 6d.

Genito-Urinary Organs, including

Syphilis : A Practical Treatise on their Surgical Diseases, for Students and Practitioners. By W. H. VAN BUREN, M.D., and E. L. KEYES, M.D. Royal 8vo, with 140 Engravings, 21s.

Lectures on Syphilis.

By HENRY LEE, Consulting Surgeon to St. George's Hospital. 8vo, 10s.

Harveian Lectures on Syphilis.

By JAMES R. LANE, F.R.C.S., late Surgeon to St. Mary's Hospital. Second Edition. Fcap. 8vo, 3s. 6d.

Urinary and Reproductive Or-

gans : Their Functional Diseases. By D. CAMPBELL BLACK, M.D. Second Edition. 8vo, 10s.

Coulson on Diseases of the

Bladder and Prostate Gland. Sixth Edition. By WALTER J. COULSON, Surgeon to the Lock Hospital and to St. Peter's Hospital for Stone. 8vo, 16s.

On Rupture of the Urinary Blad-

der. Based on the Records of more than 300 Cases of the Affection. By WALTER RIVINGTON, F.R.C.S., President of the Hunterian Society ; Surgeon to the London Hospital. 8vo, 5s. 6d.

The Reproductive Organs

In Childhood, Youth, Adult Age, and Advanced Life, considered in their Physiological, Social, and Moral Relations. By WILLIAM ACTON, M.R.C.S. Sixth Edition. 8vo, 12s.

The Medical Adviser in Life

Assurance. By E. H. SIEVERING, M.D., F.R.C.P. Second Edition. Crown 8vo, 6s.

A Medical Vocabulary :

An Explanation of all Terms and Phrases used in the various Departments of Medical Science and Practice, their Derivation, Meaning, Application, and Pronunciation. By R. G. MAYNE, M.D., LL.D. Fifth Edition. Fcap. 8vo, 10s. 6d.

A Dictionary of Medical Science:

Containing a concise Explanation of the various Subjects and Terms of Medicine, &c. By ROBLEY DUNGLISON, M.D., LL.D. New Edition. Royal 8vo, 28s.

Abridged Medical Account

Books. The "Expedite" Method. By J. MACNAB, L.R.C.S.E. *Index Ledger*. Royal 4to. For three years, 15s. *Visiting List*. Cloth, 2s. 6d. ; Leather, 3s. 6d.

Medical Education

And Practice in all parts of the World. By H. J. HARDWICKE, M.D., M.R.C.P. 8vo, 10s.

INDEX.

- Acton's Reproductive Organs, 14
 Adams (W.) on Clubfoot, 11
 on Contraction of the Fingers, 11
 on Curvature of the Spine, 11
 Alexander's Displacements of the Uterus, 6
 Allan on Fever Nursing, 7
 Allbutt's Visceral Neuroses, 9
 Allingham on Diseases of the Rectum, 14
 Anatomical Remembrancer, 3
 Anderson (McC.) on Eczema, 13
 Aveling on the Chamberlens and Midwifery Forceps, 6
 on the Influence of Posture on Women, 6
 Balfour's Diseases of the Heart and Aorta, 8
 Balkwill's Mechanical Dentistry, 12
 Barnes (E. G.) How to Arrest Infectious Diseases, 4
 Barnes (R.) on Obstetric Operations, 5
 on Diseases of Women, 5
 Beale's Microscope in Medicine, 8
 Slight Ailments, 8
 Bellamy's Surgical Anatomy, 3
 Bennet (J. H.) on the Mediterranean, 10
 on Pulmonary Consumption, 10
 on Nutrition, 10
 Bentley and Trimen's Medicinal Plants, 7
 Bentley's Manual of Botany, 7
 Structural Botany, 7
 Systematic Botany, 7
 Bigg (R. H.) on the Orthopragms of Spine, 11
 Binz's Elements of Therapeutics, 7
 Black on the Urinary Organs, 14
 Braune's Topographical Anatomy, 3
 Brodhurst's Anchylosis, 11
 Curvatures, &c., of the Spine, 11
 Orthopædic Surgery, 11
 Bryant's Practice of Surgery, 11
 Bucknill and Tuke's Psychological Medicine, 5
 Bulkley's Eczema, 13
 Burdett's Cottage Hospitals, 5
 Pay Hospitals, 5
 Burnett on the Ear, 12
 Burton's Midwifery for Midwives, 5
 Butlin's Malignant Disease of the Larynx, 13
 Sarcoma and Carcinoma, 13
 Buzzard's Diseases of the Nervous System, 9
 Carpenter's Human Physiology, 4
 Carter (H. V.) on Spillium Fever, 8
 Carter (W.) on Renal and Urinary Diseases, 14
 Cayley's Typhoid Fever, 8
 Charteris' Practice of Medicine, 8
 Clark's Outlines of Surgery, 10
 Clay's (C.) Obstetric Surgery, 6
 Clouston's Lectures on Mental Diseases, 5
 Cobbold on Parasites, 13
 Coles' Dental Mechanics, 12
 Deformities of the Mouth, 12
 Cooper's Syphilis and Pseudo-Syphilis, 14
 Coulson on Diseases of the Bladder, 14
 Courty's Diseases of the Uterus, Ovaries, &c., 6
 Cripps' Cancer of the Rectum, 14
 Cullingworth's Manual of Nursing, 7
 Short Manual for Monthly Nurses, 7
 Curling's Diseases of the Testis, 13
 Dalby's Diseases and Injuries of the Ear, 12
 Dalton's Human Physiology, 4
 Day on Diseases of Children, 7
 on Headaches, 9
 Dobell's Lectures on Winter Cough, 8
 Loss of Weight, &c., 8
 Mont Doré Cure, 8
 Domville's Manual for Nurses, 7
 Druitt's Surgeon's Vade-Mecum, 11
 Duncan on Diseases of Women, 5
 on Sterility in Woman, 5
 Dunglison's Medical Dictionary, 14
 Eade on Diphtheria, 12
 Ellis's Manual for Mothers, 6
 of the Diseases of Children, 6
 Emmet's Gynecology, 6
 Fayrer's Climate and Fevers of India, 7
 Tropical Dysentery and Diarrhoea, 7
 Fenwick's Chronic Atrophy of the Stomach, 8
 Medical Diagnosis, 8
 Outlines of Medical Treatment, 8
 Fergusson's Practical Surgery, 10
 Flint on Clinical Medicine, 8
 on Phthisis, 8
 Flower's Diagrams of the Nerves, 4
 Foster's Clinical Medicine, 8
 Fox's (C. B.) Examinations of Water, Air, and Food, 4
 Fox's (T.) Atlas of Skin Diseases, 13
 Frey's Histology and Histo-Chemistry, 4
 Galabin's Diseases of Women, 6
 Gamgee's Treatment of Wounds and Fractures, 11
 Gay on Hæmorrhoidal Disorder, 14
 Gill on Indigestion, 9
 Godlee's Atlas of Human Anatomy, 3
 Gorgas' Dental Medicine, 13
 Gowers' Diseases of the Spinal Cord, 9
 Epilepsy, 9
 Medical Ophthalmoscopy, 9
 Pseudo-Hypertrophic Muscular Paralysis, 9
 Granville on Nerve Vibration and Excitation, 9
 Habershon's Diseases of the Abdomen, 9
 Stomach, 9
 Pneumogastric Nerve, 9
 Hamilton's Nervous Diseases, 9
 Hardwicke's Medical Education, 14
 Harley on Diseases of the Liver, 9
 Harris on Lithotomy, 14
 Harrison's Surgical Disorders of the Urinary Organs, 14
 Lithotomy, Lithotripsy, &c., 14
 Hartridge's Refraction of the Eye, 12
 Heath's Injuries and Diseases of the Jaws, 10
 Minor Surgery and Bandaging, 10
 Operative Surgery, 10
 Practical Anatomy, 3
 Surgical Diagnosis, 10
 Higgins' Ophthalmic Out-patient Practice, 11
 Hill's Leprosy in British Guiana, 13
 Holden's Dissections, 3
 Human Osteology, 3
 Landmarks, 3
 Holmes' (G.) Guide to Use of Laryngoscope, 12
 Vocal Physiology and Hygiene, 12
 Hood on Gout, Rheumatism, &c., 9
 Hooper's Physician's Vade-Mecum, 8
 Horton's Tropical Diseases, 7
 Hutchinson's Clinical Surgery, 11
 Pedigree of Disease, 11
 Rare Diseases of the Skin, 13
 Huth's Marriage of Near Kin, 4
 Hyde's Diseases of the Skin, 13
 Ireland's Idiocy and Imbecility, 5
 James (P.) on Sore Throat, 12
 Jones (C. H.) Functional Nervous Disorders, 9
 Jones (C. H.) and Sieveking's Pathological Anatomy, 4
 Jones (H. McN.) Aural Surgery, 12
 Atlas of Diseases of Membrana Tympani, 12
 Spinal Curvatures, 11
 Jones (T. W.) Ophthalmic Medicine and Surgery, 12
 Jordan's Surgical Enquiries, 10
 Lancereaux's Atlas of Pathological Anatomy, 4
 Lane's Lectures on Syphilis, 14
 Lee (H.) on Syphilis, 14
 Leared on Imperfect Digestion, 9
 Lewis (Bevan) on the Human Brain, 4
 Liveing's Megrim, Sick Headache, &c., 10
 Macdonald's (A.) Chronic Disease of the Heart, 6
 Macdonald's (J. D.) Examination of Water and Air, 4
 Macewen's Osteotomy: Knock-Knee, Bow-Leg, &c., 11
 Mackenzie on Diphtheria, 12
 on Diseases of the Throat and Nose, 12
 MacLise's Dislocations and Fractures, 10
 Surgical Anatomy, 3
 MacMunn's Spectroscope in Medicine, 8
 Macnab's Medical Account Books, 14
 Madden's Principal Health-Resorts, 10
 Mann's Manual of Psychological Medicine, 5
 Marcet's Southern and Swiss Health-Resorts, 10
 Marsden's Certain Forms of Cancer, 13
 Mason on Hare-Lip and Cleft Palate, 12
 on Surgery of the Face, 12
 Mayne's Medical Vocabulary, 14
 Notes on Poisons, 7
 Therapeutical Remembrancer, 7
 Moore's Family Medicine for India, 7
 Health-Resorts for Tropical Invalids, 7
 Morris' (H.) Anatomy of the Joints, 3
 Mout and Snell on Hospitals, 5
 Nettleship's Diseases of the Eye, 12
 Nunn's Cancer of the Breast, 13
 Ogston's Medical Jurisprudence, 4
 Oppert's Hospitals, Infirmarys, Dispensaries, &c., 3

(Continued on the next page)

INDEX—continued.

- Osborn on Diseases of the Testis, 14
 — on Hydrocele, 14
 Owen's *Materia Medica*, 7
 Page's Injuries of the Spine, 11
 Parkes' *Practical Hygiene*, 5
 Pavy on Diabetes, 9
 — on Food and Dietetics, 9
 Pharmacopœia of the London Hospital, 7
 Phillips' *Materia Medica and Therapeutics*, 7
 Pollock on Rheumatism, 9
 Porritt's Intra-Thoracic Effusion, 8
 Pridham on Asthma, 8
 Purcell on Cancer, 13
 Quinby's Notes on Dental Practice, 13
 Ralfe's Morbid Conditions of the Urine, 14
 Ramsbotham's *Obstetrics*, 6
 Raye's *Ambulance Handbook*, 10
 Reynolds' (J. J.) *Diseases of Women*, 6
 — Notes on Midwifery, 6
 Rivington's Rupture of the Urinary Bladder, 14
 Roberts' (C.) *Manual of Anthropometry*, 5
 — Detection of Colour-Blindness, 5
 Roberts' (D. Lloyd) *Practice of Midwifery*, 5
 Ross's *Diseases of the Nervous System*, 9
 Roth on Dress: Its Sanitary Aspect, 4
 Routh's Infant Feeding, 6
 Royle and Harley's *Materia Medica*, 7
 Sanderson's *Physiological Handbook*, 4
 Sansom's *Diseases of the Heart*, 9
 Savage on the Female Pelvic Organs, 6
 Sayre's *Orthopaedic Surgery*, 11
 Schroeder's *Manual of Midwifery*, 6
 Sewill's *Dental Anatomy*, 12
 Sheppard on Madness, 5
 Sibson's *Medical Anatomy*, 3
 Sieveking's *Life Assurance*, 14
 Smith's (E.) *Clinical Studies*, 6
 — Wasting Diseases of Infants and Children, 6
 Smith's (Henry) *Surgery of the Rectum*, 14
 Smith's (Heywood) *Dysmenorrhœa*, 6
 Smith (Priestley) on Glaucoma, 12
 Snell's *Electro-Magnet in Ophthalmic Surgery*, 11
 Snow's *Clinical Notes on Cancer*, 13
 Southam's *Regional Surgery*, 10
 Sparks on the Riviera, 10
 Squire's *Companion to the Pharmacopœia*, 7
 — *Pharmacopœias of London Hospitals*, 7
 Starkweather on the Law of Sex, 4
 Stillé and Maisch's *National Dispensatory*, 7
 Stimson on Fractures, 11
 Stocken's *Dental Materia Medica and Therapeutics*, 13
 Swain's *Surgical Emergencies*, 10
 Swayne's *Obstetric Aphorisms*, 6
 Taylor's *Medical Jurisprudence*, 4
 — Poisons in relation to Medical Jurisprudence, 4
 Teale's *Dangers to Health*, 4
 Thompson's (Sir H.) *Calculus Disease*, 12
 — Diseases of the Prostate, 13
 — Diseases of the Urinary Organs, 13
 — Lithotomy and Lithotripsy, 13
 — Tumours of the Bladder, 13
 Thompson's (Dr. H.) *Clinical Lectures*, 8
 Thorowgood on Asthma, 9
 — on *Materia Medica and Therapeutics*, 7
 Thudichum's *Pathology of the Urine*, 14
 Tibbits' *Medical and Surgical Electricity*, 10
 — Map of Motor Points, 10
 Tidy and Woodman's *Forensic Medicine*, 4
 Tilt's *Change of Life*, 6
 — Uterine Therapeutics, 6
 Tomes' (C. S.) *Dental Anatomy*, 12
 Tomes' (J. and C. S.) *Dental Surgery*, 12
 Tosswill's *Diseases and Injuries of the Eye*, 11
 Tuke's *Influence of the Mind upon the Body*, 5
 — Sleep-Walking and Hypnotism, 5
 Van Buren on the Genito-Urinary Organs, 14
 Vintras on the Mineral Waters, &c., of France, 10
 Virchow's *Post-mortem Examinations*, 4
 Wagstaffe's *Human Osteology*, 3
 Walker's *Ophthalmology*, 11
 Waring's *Indian Bazaar Medicines*, 7
 Warner's *Guide to Medical Case-Taking*, 8
 Warren's *Hernia and Rupture*, 11
 Waters' (A. T. H.) *Diseases of the Chest*, 8
 Waters (J. H.) on Fits, 9
 Wells (Spencer) on Ovarian and Uterine Tumours, 6
 West and Duncan's *Diseases of Women*, 6
 West (S.) *How to Examine the Chest*, 8
 Whistler's *Syphilis of the Larynx*, 12
 Whittaker's *Primer on the Urine*, 14
 Wilks' *Diseases of the Nervous System*, 9
 Wilks and Moxon's *Pathological Anatomy*, 4
 Wilson's (Sir E.) *Anatomists' Vade-Mecum*, 3
 — Lectures on Dermatology, 13
 Wilson's (G.) *Handbook of Hygiene*, 5
 — Healthy Life and Dwellings, 5
 Wilson's (W. S.) *Ocean as a Health-Resort*, 10
 Wolfe's *Diseases and Injuries of the Eye*, 11
 Yeo (G. F.) *Manual of Physiology*, 4
 Yeo (J. B.) *Contagiousness of Pulmonary Consumption*, 8
 Zander Institute *Mechanical Exercises*, 10

The following CATALOGUES issued by J. & A. CHURCHILL will be forwarded post free on application:—

A. J. & A. Churchill's *General List of about 650 works on Anatomy, Physiology, Hygiene, Midwifery, Materia Medica, Medicine, Surgery, Chemistry, Botany, &c., &c., with a complete Index to their Subjects, for easy reference.* N.B.—This List includes B, C, & D.

B. *Selection from J. & A. Churchill's General List, comprising all recent Works published by them on the Art and Science of Medicine.*

C. J. & A. Churchill's *Catalogue of Text Books specially arranged for Students.*

D. *A selected and descriptive List of J. & A. Churchill's Works on Chemistry, Materia Medica, Pharmacy, Botany, Photography, Zoology, the Microscope, and other branches of Science.*

E. *The Half-yearly List of New Works and New Editions published by J. & A. Churchill during the previous six months, together with particulars of the Periodicals issued from their House.*

[Sent in January and July of each year to every Medical Practitioner in the United Kingdom whose name and address can be ascertained. A large number are also sent to the United States of America, Continental Europe, India, and the Colonies.]

AMERICA.—J. & A. Churchill being in constant communication with various publishing houses in Boston, New York, and Philadelphia, are able, notwithstanding the absence of international copyright, to conduct negotiations favourable to English Authors.

LONDON: NEW BURLINGTON STREET.



J53 Thudichum, J.L.W. 17046
T53 The pathology of the
1877 urine. 2d ed.

NAME

DATE DUE

